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SCIENTIFIC MEETING

Honorary Convener: A. J. WRIGLEY, M.D., F.R.C.S., F.R.C.O.G.

held in the

NUFFIELD HALL

of the

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

on

Thursday, 14th July and Friday, 15th July, 1960

PROGRAMME

Thursday, 14th July

The President announced the gift from Sir Eardley Holland of a GOLD MEDAL to be awarded every five years for original work of outstanding merit in obstetrics and gynaecology, or for outstanding work as a practitioner, author or teacher.

Sir Eardley Holland made the first award to Professor John Chassar Moir for his work in the discovery of Ergometrine.

Sir Henry Dale was present by invitation (*page* 752).

THE PATHOLOGY AND TREATMENT OF MALIGNANT GLANDULAR METASTASES OF THE LATERAL PELVIC WALL (*page* 709)

Chairman: Dr. D. F. STANDING (Durban)

Opening Speakers: Dr. WARING G. COSBIE (Toronto), Dr. A. D. CAMPBELL (Montreal) and Dr. ARTHUR M. HILL (Melbourne)

The President received gifts offered to the College to commemorate the opening of the new building.

A DISCUSSION ON THE FUTURE ACTIVITIES OF THE COLLEGE (*page* 754)

Chairman: Mr. J. N. CHESTERMAN (Sydney)

Opening Speakers: Professor JAMES LOUW (Cape Town), Mr. H. R. MACLENNAN (Glasgow) and Mr. A. C. H. BELL (London)

Friday, 15th July

THE USE AND ABUSE OF ANTIBIOTICS (*page* 726)

Chairman: Dr. A. B. NASH (Victoria, B.C.)

Introduction by Professor RONALD HARE

Opening Speakers: Dr. MARY BARBER (London), Dr. B. W. LACEY (London) and Dr. T. F. CORKILL (Wellington, New Zealand)

HAEMOLYTIC DISEASE OF THE NEWBORN (*page* 740)

Chairman: Dr. T. F. CORKILL (Wellington, New Zealand)

Introduction by Professor ALAN MONCRIEFF

Opening Speakers: Mr. F. E. STABLER (Newcastle-on-Tyne) and Dr. A. P. NORMAN (London)

THE PATHOLOGY AND TREATMENT OF MALIGNANT GLANDULAR METASTASES OF THE LATERAL PELVIC WALL

BY

W. G. COSBIE, M.B., F.R.C.S.(C.), F.R.C.O.G.
Medical Director
The Ontario Cancer Treatment and Research Foundation

AND

WM. ANDERSON, M.B., Ch.B.
Associate Professor
Department of Pathology, University of Toronto

EVER since it was recognized that cells of a malignant tumour possess an inherent tendency to spread and to involve tissues at some distant site pathologists have attempted to determine a pattern for this extension and therapists have striven to develop methods of treatment to control it. The survival of patients in whom extension had occurred has been studied in order to determine the prognostic significance of this feature of malignant disease. However, in view of the intricate and variable nature of human physiology and the dependency of all living tissue on biological controls, the dissemination patterns have been shown to display a not unexpected diversity.

So long as a malignant tumour remains localized there is little argument among clinicians as to acceptable methods of treatment. Handley's dictum that lymphatic spread is the major path of carcinomatous dissemination has long been the basis for accepted surgical techniques. It is well known, however, that the lymphatics represent only one of several routes of spread and in many cases blood-borne metastases occur while lymphatic involvement is hardly recognizable. It is also true that whereas with most tumours there is a certain sequence in the involvement of lymphatic tissue, exceptions are frequent and unpredictable.

In the case of female genital cancer, metastasis to the pelvic lymph nodes presents a major problem. It is generally recognized that involvement of the nodes is largely a mechanical process, cells shed by the tumour being carried in the lymph stream. It has been suggested that manifestations of host resistance may be encountered in the lymph nodes, but there is no evidence of destruction of cancer cells by lymphoid tissue and it appears, rather, that the arrested cells profit by being located in a nutrient focus. The affected nodes may remain discrete for varying periods of time, the growth being confined within the gland capsule, but sooner or later groups of glands tend to coalesce as the result of extracapsular infiltration and occlusion of the connecting lymphatics. Haemic dissemination, if not a primary phenomenon, follows as a complication of the extension from involved lymph nodes. Thus the filter which at first tended to localize particulate matter picked up from the extra-cellular fluid may itself become a fortuitous nidus for the further spread of cancer.

It will be recalled that neither Wertheim nor Schauta, in presenting the classical operations which bear their names, laid stress on the need to remove the lymph nodes. Wertheim satisfied himself by removing palpably enlarged nodes and this principle has governed the work of the Vienna School until very recently. Victor Bonney (1941), on the other hand, considered the involvement of the lymph nodes by tumour

a much more reliable criterion of an unfavourable state than the clinical staging used by radiotherapists, and he presented the incidence of involvement and the effect it had on operative mortality and the ultimate survival of the patient.

For a long time in America, neither in the United States nor in Canada, was there anyone who gave leadership in the manner of Victor Bonney. He and his school, as exemplified by his brilliant disciple, Charles Read, maintained the place of surgery even while British radiotherapy was developing the methods of precision which were its greatest contribution to the treatment of cervical cancer. It was not until J. V. Meigs (1951, 1954), dispelled the cloud of apprehension which shrouded the surgical treatment of this lesion that surgery came back to its proper place in the minds of American gynaecologists. Meigs demonstrated that under modern conditions, radical hysterectomy and pelvic lymphadenectomy could be performed with a minimum of operative mortality. He also established the fact that whereas the removal of involved lymph nodes contributed to a high salvage rate when the primary lesion was limited to the cervix, this did not apply to lesions which had extended into the paracervical and paravaginal tissues. Meigs' early teaching that surgery provided the only means of controlling involved lymph nodes gained considerable support for the opinion originally held by Bonney. This is an opinion which has altered slowly over the passage of many years.

Lymphadenectomy has never been widely adopted as an adjunct to radiotherapy. In 1943 F. J. Taussig of St. Louis reported on a series of 175 transperitoneal lymphadenectomies performed after radiotherapy. The incidence of involved nodes was 26·8 per cent and 21 per cent of these patients survived five years. A few years later, D. G. Morton (1947), reporting on a small group of patients, compared an incidence of 35·5 per cent with involved nodes in primary surgical patients with only 11·4 per cent in those who had received previous radiotherapy. It should be realized that in those days radiotherapy for cancer of the cervix depended on the effect of radium applied within the cervical canal and to the vault of the vagina, and that this method delivered only a very small dose to the gland-bearing areas. Supplementary external irradiation was delivered through multiple ports in an effort to build up further the irradiation of the immediate paracervical and paravaginal tissues. Little consideration was given to the irradiation of the tissues at the side wall of the pelvis. In recent years Gorton (1957), has presented the only large series of cases so treated. He reported on 364 extraperitoneal lymphadenectomies and noted an incidence of 30 per cent and 13·6 per cent of node involvement, the difference depending on the use of previous radiotherapy. He found that there was not a constant relation between persistent local disease after radiotherapy and node involvement. Although he showed that the five-year survival in Stage I and II lesions was increased, he felt some doubt as to the justification of the combined procedure because of the morbidity and mortality which followed it, and the deaths which occurred of patients with involved nodes despite adenectomy.

The extensive operation, originally described by Brunschwig, by which the pelvic viscera are removed *en masse* when cervical cancer has extended to involve the bladder and/or rectum, or laterally so as to have encompassed the ureters and to have reached the side walls of the pelvis, is justified by the fact that in only 50 per cent of cases is there macroscopic evidence at post-mortem of the spread of cancer beyond the pelvis. It has become increasingly evident that lymph node involvement is of the gravest prognostic significance in extensive lesions. This is especially true in those cases when exenteration is undertaken after radiotherapy has proven ineffective in controlling cancer of the cervix. It is only in the last eighteen months that Brunschwig has been able to report any five-year survivals when involved nodes have been present at exenteration after radiotherapy. However, with a change in policy, namely, doing fewer exenterations when it is doubtful whether all of the disease can be removed and applying the operation to more Stage IIB lesions, he now reports that eight patients with positive nodes operated upon for persistent disease after radiotherapy, survived over five years. Parsons' experience (1959a) has been similar and in a recent report on 120 patients treated by exenteration, of whom 74 allow a five-year appraisal, he had an operative

mortality of 22·5 per cent with a five-year survival of 24 per cent. Fifty per cent survived five years when the nodes were not involved and none when they were; and he considers that lymph node involvement is the largest single factor in determining prognosis. Both Bricker (1960) and Ulfelder (1960), as the result of considerable experience, hold this same opinion with regard to the grave significance of lymph node involvement associated with widely extensive primary lesions. As a matter of fact, Bricker considers that involvement of para-aortic nodes precludes operation.

In a recent publication Parsons (1959b) has drawn attention to the fact that too much emphasis may be laid on lymph node dissection, while at the same time the primary lesion is being dealt with inadequately. The intricate relations of the lymph channels draining the cervix and the base of the bladder are such as to permit extension of the growth anteriorly while the lateral spread remains at a minimum. Parsons concludes that the surgeon undertaking the treatment of cervical cancer must be prepared to extend hysterectomy to exenteration, reiterating the principle advanced by Brunschwig and Daniel (1958). The alternative to exenteration must be radiotherapy.

The Editor (Jones, 1960) of *Obstetrical and Gynecological Survey* has presented further valuable evidence in the critical appraisal of the place of lymphadenectomy in the treatment of cervical cancer in a review of a recent publication of Rauscher and Spurny (1959) of Vienna, in which these authors present a table (see Table I), which shows that there has been little difference in the survival rate stage for stage, with or without lymphadenectomy.

The group treated without lymphadenectomy received post-operative radiotherapy. If this is to be considered a curative factor, then it appears that the pendulum has swung to full extent, and now post-operative radiotherapy under reversed conditions has replaced post-radiotherapy lymphadenectomy in providing an increased survival rate.

During the last twenty years, radiotherapy for pelvic cancer has become much more effective. Radiation physics has become an integral part of the treatment routine and, as a result, accurate

TABLE I*

Relative Cure in 315 Patients with Cervix Carcinoma

Without Obligatory Lymphadenectomy, Operated between May 1947 and May 1950

Stages	Operated	5-Year Cure	Per cent
I	88	72	81·81
II	68	45	66·17
III	2	0	0·00
	158	117	74·05

With Obligatory Lymphadenectomy, Operated between May 1950 and May 1953

Stages	Operated	5-Year Cure	Per cent
I	95	83	87·37
II	62	36	58·03
III	0	0	0·00
	157	119	75·79

* This table is reproduced with the permission of the Editor of *Obstetrical and Gynecological Survey*.

beam direction and depth dose mensuration and the use of mega-voltage equipment has made it easy to deliver a cancer-lethal dose to the gland-bearing areas, while the central area of the pelvis, adequately screened from excessive external irradiation, is treated satisfactorily by radium sources in the cervix and vaginal vault. The experience of the radiotherapy centres of the Ontario Cancer Foundation, who reviewed over 4,000 cases of cervical cancer in October 1959, indicates a marked improvement in the five-year survival rate which had risen from 33·3 per cent to 45·6 per cent in this period of time. The greatest relative improvement occurred in the Stage II and Stage III lesions, which was three-and-a-half and four times greater respectively than that of the Stage I lesions. It must be admitted that the situation with regard to the latter group has undoubtedly been modified by the increasing number of patients who have been treated surgically. Otherwise, considering all the factors involved, one might suggest that the success with the more extensive lesions may indicate an increasing control of cases with pelvic lymphatic metastases. But, on the other hand, the death of half the patients with Stage II

and three-quarters of those with Stage III lesions is the basis for an opposite opinion, that the controlled cases represent ones without lymph node involvement.

A year ago, at Cardiff, Windeyer (1959) stated that now that it is possible with improved quality of irradiation to deliver an adequate homogeneous dose to the whole pelvis it may be preferable to omit intracavitary radium and do the whole treatment by super-voltage beam. Watson (1960), of Saskatoon, has treated a series of cases on this principle, using a 22 Mev. betatron, and while he admits the risk of over-irradiating bowel, bladder and neck of femur, he has shown improved results in a small number of advanced lesions. Watson concluded that the determining factor, as far as success or failure in treatment is concerned, is the inherent radiosensitivity of the tumour, in which there may be little difference between the primary growth and the secondary deposits.

Rutledge and Fletcher (1958) have reported on the results of lymphadenectomy on a group of 100 patients with Stage III lesions who had been treated three months previously with this type of irradiation, and found only 22 per cent with involved nodes compared to the generally accepted 46·5 per cent; and excluding nodes at or above the brim of the pelvis only 14 per cent had nodal involvement, that is within the irradiated area. Probably the most interesting observation was the variation in response to treatment in different nodes in the same patient, some showing evidence of destruction of the cancer cells while others showed viable cancer still present.

Kottmeier (1953, 1957), with his great experience at Radiumhemmet, feels that while there is no doubt that local disease in the cervix requires a heavy dose of irradiation, he does not believe that it has been proven that a dose of 5,000 to 6,000 roentgens to the whole pelvis in six to eight weeks is required to cure carcinoma which has invaded the parametrium or has given rise to lymph node metastases. The chance of destroying lymph node metastases is not, in his opinion, proportionate to the applied dose of radiation. It has never been proven that a dose adequate to control a tumour is the same for all its parts, for several radiotherapists have observed that the dose to destroy a carcinoma is less in the periphery than in the central part of the tumour, and he quotes Sievert, "Today physicists sometimes concentrate too much on problems in which medical experience has already arrived empirically at a satisfactory solution." The problem then becomes one for the biophysicist, or as Kottmeier observes, "It is obvious that the direct effect of ionizing rays upon cells is important, but I am convinced that also the indirect effect, the host response, is of great significance."

The factors which govern the behaviour of any malignant process continue to present an unanswerable problem. Friedell and Graham (1959), when they attempted to show the critical size of cervical cancer at which lymph node involvement occurred, learned from a final case that this could not be determined. The Grahams (1955, 1960), however, have presented evidence to indicate that an increased lymph node involvement is associated with the group of patients showing a high sensitization reaction and, interestingly, the finding of a high S.R. is held by them to indicate those cases in which radiation should be preferable to surgery. Recently, they have also published a report indicating that the desquamation of malignant cells, as seen in vaginal smear, is a phenomenon that is correlated with the incidence of regional metastases. At the present time all these observations have merely a relative value.

Finally, the discovery by a number of investigators that the cell population of tumours on the basis of their chromosomal numbers is not homogeneous, but is heterogeneous, is of great significance in explanation of the difference in the resistance of neoplasms to therapy. The destruction of the predominant cell types may result in a change in the cell population, whereby the proportion of a variant cell increases so that the neoplasm no longer responds to the therapy which previously appeared to control the situation. It is also possible that the dynamic equilibrium which governs the nature of a tumour or its metastases alters in time, so that in the ageing process a tumour which was radiosensitive alters in its response. This concept may also apply to the greater aggressiveness which different tumours may show from time to time

as evidenced by the development of both lymphatic and haemic metastases.

The failure to control lymph node metastases by surgery depends to no small degree on the difficulty of performing anything more than as Meigs says, "at best a crude dissection of the pelvic nodes. Certainly there are so many chains and so many nodes in each chain that it would be impossible to remove them all." After reviewing 55 post-mortems performed on patients who had Wertheim hysterectomy, with and without lymphadenectomy, anterior or total exenteration, Kelly and ot' .s (1960) concluded that node involvement indicates that cancer has reached the stage when it has begun to spread *via* one or more alternate routes. Faced with this situation it becomes apparent that our concept of the control of malignant disease originating in the female pelvis must not be limited to any solitary facet of the problem irrespective of its apparent immediate importance.

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THE PATHOLOGY AND TREATMENT OF MALIGNANT GLANDULAR METASTASES OF THE LATERAL PELVIC WALL—*continued:*

ARCHIBALD D. CAMPBELL, M.D., C.M., F.R.C.S.(Canada), F.A.C.S.
Associate Professor of Obstetrics and Gynaecology
McGill University, Montreal

(Assisted by Doctors P. R. Blakey, E. A. MacCallum, D. D. Munro and C. C. Lindsay)

CARCINOMA of the female reproductive tract has continued to exact its relatively unchanged annual death toll, in spite of the refinements in physical treatment that have been witnessed since the formation of this College. It is estimated that, in the U.S.A., approximately 25,000 women yearly present themselves for some form of genital cancer. In Canada, with a population of some 15,000,000, there are annually 650 deaths from carcinoma of the cervix and 450 from that of the corpus.

A woman affected with pelvic cancer has a less than 50 per cent chance of living five years, no matter how treated. If she survives this span, she is presumed to have a 60–70 per cent chance of living 10 years after discovery of the disease. The inability to improve appreciably the survival, no matter what type or combination of types of treatment are used, demands a reappraisal of the problem. Certainly where the lesion is local, treatment results are satisfactory; but where there is invasion of the regional lymph nodes, results are disappointing. It is fitting, therefore, that gynaecologists should reflect on the more serious category of genital cancer, where it has spread to the lymphatic nodes of the lateral wall of the pelvis. Consideration of the pathological processes along with treatment employed and results obtained seems the only way to improve survival until some specific agent to cure cancer is discovered.

Female genital cancer spreads from its site of origin, by direct extension, by the lymphatics and by the blood stream. Our knowledge of the lymphatic system and its role in the spread of cancer is imperfect. It is interesting to note that the lymphatic system comprises one per cent of the body weight. The lymph node itself contains masses of lymphocytes, occupying the periphery of the node, with cells of the reticulo-endothelial system situated along its trabeculae.

The lymph nodes obviously serve to arrest migratory cells and are abundant in the young and sparse in the aged. Just how the nodes of one individual may be more resistant to cancer invasion than those of another is not known. Beta and gamma globulin fractions are produced and stored within the tissue of the reticulo-endothelial system, along with other protein fractions, as yet unidentified, entering into immunologic reaction. This suggests that host response is an important consideration, but it has as yet defied clinical assessment. It is known, however, that immunologic response may be mediated through the pituitary-adrenal axis, the endocrine elaborations of which have come under increasingly wide scrutiny of late. As old age approaches, it would seem that there is less demand on the lymphatics as an active protective mechanism. Natural regression of the activity of the endocrine system, which occurs from the fifth decade onward, possibly in part accounts for the slow spread of carcinoma in this group as compared with those of an earlier age.

Although not of constant arrangement, recognized lymph node stations are described. These are situated in relation to the external iliac vessels, the internal iliac vessels, the utero-sacral ligaments, the inferior vesical vessels, the inguinal areas and the obturator fossae. No two individuals have precisely the same lymphatic arrangement. Were the lymphatic system more constant, or were it possible to identify its channels, we would have a clearer idea as to the direction of spread of malignancy and be able to apply appropriate treatment more intelligently.

Assessment of cancerous involvement of the nodes by physical examination is lacking in precision. Peripheral inflammatory reaction is difficult to differentiate from neoplastic infiltration. Malignancy spreads by devious routes.

Retrograde spread is acknowledged and central spread of disease does not necessarily involve successive node stations. On the other hand, inflammation in the absence of malignancy spreads in a more predictable pattern. This may be exemplified by the early involvement of the femoral nodes in carcinoma of the vulva, while these are rarely affected in vulval inflammation.

Where a local tumour is small and infiltration is not appreciable, node involvement may have already occurred. Wertheim in 1905, in his classical studies, demonstrated that there was nodal involvement in 10 per cent of the cases of cancer of the cervix, yet the parametrium was free from malignant cells. On the other hand, it has been pointed out recently that the tissues of the paravaginal and paracervical area are often infiltrated with cancer without nodal involvement.

At autopsy 50–70 per cent of the nodes of the lateral pelvic walls are involved. At operation node involvement in early cases is encountered in 20 per cent of cases. Both Langdon Parsons of Boston and A. Brunschwig of New York have emphasised that local spread or recurrence of carcinoma of the cervix, treated by irradiation, has been demonstrated in the paracervical, paravaginal, uterosacral, inferior vesical and obturator node areas. Parsons has shown a 12–18 per cent incidence of node involvement even in Stage I carcinoma of the cervix. These vagaries of node involvement in cancer of the female genitalia have long been recognized.

In 1910, Dr. Archibald Leitch observed that "malignancy may be early with regard to duration, but late in respect to dissemination", and similarly, Sir Comyns Berkeley stated that "enlarged glands do not necessarily indicate malignant invasion while there may be early deposits in glands barely palpable". The assessment of the role of node involvement in cancer in the female pelvis always has been a thorny problem. Granting that appraisal of tumour potentialities in the nodes is difficult, it is equally difficult to assess malignant potentialities by histological means. The histological pattern of cells within a mass of malignancy often gives little indication of its proclivities. Many histological criteria have been examined in the attempt to predict the tendencies of an individual tumour.

While histological patterns of malignant cells may seem microscopically to be identical, the biological behaviour of those cells is quite different. In one individual these cells may multiply and remain as a local disease, yet in others metastasis occurs early with or without node involvement. In effect, a cancer cell is genetically different from other cells of the host and carcinomatous cells differ within a tumour mass itself.

The one common factor in carcinoma is that it is more apt to develop in those tissues with a rapid physiological replacement of its components. Some invade, others migrate, while others develop locally. A certain percentage of patients with comparable malignant lesions succumb to the disease while others survive. There must exist, therefore, some resistance or immunity factor, as yet unknown, in the host.

Mutation may be initiated by many agents which are reputed to be carcinogenic. The resistance of the host to specific forms of malignant cells undoubtedly influences their behaviour. The patient may, for even a long period of time, resist progress of the disease, but it cannot be assumed that she is permanently free from the stigma of cancer. It has been recently shown that cancer cells frequently can be isolated from the blood stream and bone marrow in patients with a malignant lesion. Engle of Stockholm feels that there is a relationship between blood-borne malignant cells and survival, but indicates that the number of cells so found was related to the degree of operative trauma. Haematogenously borne cells may persist for a considerable period after the primary lesion is thought to have been removed. The fact that the yield of cancer cells is not constant and of varying and diminishing numbers, suggests the presence in the host of some agent inimical to their propagation causing the blood-borne cells to perish. The importance of host reactivity has been demonstrated in the laboratory animal which can be immunized against a viral cancer. The development of malignancy is not an acute process.

The recognition of exfoliated malignant cells from the cervix has been responsible for bringing cases otherwise not suspected within the orbit of the gynaecologist. Cervical smears show the

presence of malignant cells in approximately one half of 1 per cent of routine examinations. In many of these there are no signs nor symptoms. Dr. Ruth Graham of Buffalo, in observing certain characteristics within exfoliated malignant cells, is able to predict with reasonable accuracy those cells that are radio-sensitive from those that are probably radio-resistant.

In the realm of treatment, marginal advances have occurred in the past two decades. Supportive measures have allowed more radical surgery. Radiotherapeutic techniques have become more precise, whilst chemotherapy, although by no means specific, has prolonged life with a degree of palliation.

There has been restoration of interest in the role of surgery and in surgery of the more radical type. Dr. Joseph V. Meigs, an exponent of total hysterectomy with lymphadenectomy in treatment of carcinoma of the cervix, has reawakened American interest in this method of therapy. The use of surgery to replace irradiation is, however, constantly under examination and remains controversial. The relative roles of surgery and irradiation, in the light of present knowledge, would seem to depend on the following factors: (1) extent of disease; (2) host resistance; (3) condition of patient; (4) skill and training of the surgeon and radiotherapist.

In the treatment of carcinoma of the vulva, the superiority of surgery is conceded. Here the management of the regional lymph nodes presents more of a problem as cancer of the vulva is seen mainly in the elderly woman, who may or may not tolerate surgery well. Therefore, the condition of the patient and the degree of dissemination of the disease, as evidenced by nodal involvement, determines the extent of the procedure.

In dealing with carcinoma of the cervix, although there has been a renewed interest in the role of surgery, our attempts at the Montreal General Hospital have been directed towards improvement of radio-therapeutic technique. It has been our impression that, with the acquisition of the radioactive cobalt and caesium bombs, the survival of patients with disease spread to the lateral pelvic nodes has been improved.

Dr. Peter Blahey, one of my associates, has developed a semi-rigid applicator for intra-cavity irradiation which provides a fixed relationship of vaginal and intra-uterine sources, both to each other and to the pelvic basin. This allows of variation within the applicator to produce similar isodose curves no matter what anatomical variations exist. The results of this change in technique would appear promising. (See Figures 1, 2 and 3.)

Radical surgery in the treatment of carcinoma of the cervix has been reserved in our clinic for recurrence after irradiation. Our difficulties in this respect have been those usually quoted, namely, the early diagnosis of recurrence. Histological diagnosis by biopsy may be difficult and does not always ensure early recognition of recurrence. In our hands cytological examination of exfoliative cells by the method of Papanicolaou, as a follow-up procedure after irradiation of carcinoma of the cervix, has not been satisfactory.

Difficulties in managing lateral pelvic node involvement in cases of cancer of the uterine corpus may be solved in part by the nature of the spread of the disease. It tends to remain local in the uterus for a considerable time, where efficient treatment should suffice, be it surgical, irradiation, or a combination of these. Where nodes are involved on the lateral pelvic wall, the para-aortic nodes are potentially involved so that radical pelvic operation would not encompass the disease.

In the controversy over the relative merits of surgery and irradiation in the treatment of pelvic node metastases, one must consider the possible deficiencies of any chosen treatment. Surely the surgeon's scalpel has no microscopic eye to distinguish healthy from cancerous tissue. It may even damage healthy tissue just as does irradiation. This scalpel, therefore, if it does not entirely remove the cancerous tissue, may activate and spread disease. Also in the present light of knowledge, the gynaecologist must accept the fact that many patients under his care for cancer may have viable but arrested tumour cells present. There is no agent yet at hand which will selectively kill cancerous growth with no damage to the host tissue.

If a patient has persisting active disease, the gynaecologist in adopting treatment should be reasonably sure that it is not going to produce

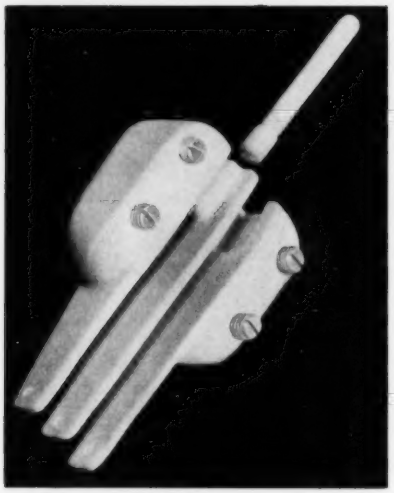

FIG. 1

Applicator for uterine tandem with double vaginal parallel radium pattern. This applicator obviates vaginal packing.

FIGS. 2 AND 3

Antero-posterior and lateral X-ray film of uterine tandem with double vaginal parallel radium pattern showing radium in place.

consequences more incapacitating than the disease itself. The impulse to perform a radical surgical procedure at this juncture should not be undertaken without dispassionate appreciation of the possible consequent physical and psychological disabilities.

Assuming that radical surgery is the treatment of choice, such is available to a relatively small percentage of our pelvic cancer population. The obvious reason for this is that there are all too few surgeons who have the necessary clinical knowledge, the patience or natural surgical aptitude. The appalling number of sub-total hysterectomies performed with its high incidence of malignancy developing in the neglected stump bears witness to this fact.

Though the nodes may be involved and removed surgically, there undoubtedly remain malignant cells within the adjacent cellular tissue. While nodes may and do cause temporary arrest in the migration of cells, these are unfortunately often by-passed. The merit in surgery, therefore, probably lies as much in the destruction of lymphatic channels as in the removal of nodes *per se*. Can it not be postulated that adequate irradiation provides a similar destruction with obliteration of the pelvic lymphatic chains?

Sir Comyns Berkeley in 1909 emphatically stated: "It is impossible to remove from the living woman all the glands that drain the pelvic organs—there is no means either from appearance, size or consistency, of clinically diagnosing glands which are invaded by cancer cells."

In the treatment of carcinoma, therefore, no matter what form of therapy is employed, there are at least four unknown factors: (1) cause of cancer; (2) the inherent character of the cells; (3) the resistance of the patient; (4) a combination of these last two.

The resistance of the host to specific forms of malignant cells undoubtedly influences their behaviour. The figures of carcinoma-control programmes indicate that surgery or irradiation, no matter how early or skilfully applied, does not prevent the extension of highly malignant cells, nor obviate their metastasis. Therapeutic failure must be accepted in a certain percentage of cases.

It is my considered opinion that malignancy should be a reportable disease. By the establishment of state institutions supplied with the most advanced scientific equipment and manned by scientists and clinicians of the highest order, there is hope that, by such a programme, eventually the cause of malignancy may be identified. This is the first phase in its treatment. While awaiting this goal, we must continue with and improve the presently well-tried methods which the individual gynaecologist is best qualified to employ.

THE PATHOLOGY AND TREATMENT OF MALIGNANT GLANDULAR METASTASES OF THE LATERAL PELVIC WALL—*continued:*

ARTHUR M. HILL, M.D., D.G.O., F.R.C.S.E., F.R.C.O.G.
Honorary Gynaecologist
The Royal Women's Hospital, Melbourne

THIS report is based on the clinical and pathological findings in 507 patients who had pelvic lymphadenectomy performed during treatment for uterine cancer at The Royal Women's Hospital, Melbourne, in the 10 years ending 31st December, 1959. The number comprises 415 women who had cancer of the uterine cervix, with pelvic lymph gland metastases in 24 per cent, and 92 who had cancer of the uterine body, with pelvic lymph gland metastases in 11 per cent.

PATHOLOGICAL FINDINGS

(1) There were 100 patients with pelvic lymph gland metastases due to cervical cancer. In 53 of these, the glands at operation were thought to contain carcinoma; in 15 there was glandular enlargement which was regarded as inflammatory; and in 32 the glands appeared to be normal. The criteria of malignancy were hardness, enlargement, irregularity or fixity; those of inflammation were regular enlargement, mobility,

TABLE I

Cervical Cancer: Sites and Distribution of Lymph Gland Metastases

No. of Patients	Distribution		Sites					
	Multiple	Bilateral	External Iliac	Obturator	Internal Iliac	Common Iliac	Sacral (para- and post-rectal)	Ureteric
49 (alive) ..	17	13	27	23	8	6	3	2
51 (dead) ..	35	27	32	27	27	15	6	1
Total 100 ..	52	40	59	50	35	21	9	3

and soft or rubbery consistency. The groups most often involved were the external iliac and obturator, less often the internal iliac, common iliac and sacral, and the ureteric gland only rarely (Table I). Metastases in more than one group of glands, or on both sides of the pelvis, were twice as common among patients who died.

There were 10 patients with pelvic lymph gland metastases due to cancer of the uterine body. More than one group of glands contained metastases in 6 patients, and in 3 the metastases were bilateral. The groups involved were the obturator in 5 patients, common iliac in 5, internal iliac in 3, and external iliac in 3.

(2) In all cases the microscopic structure of the tumour in the lymph glands was essentially the same as that of the primary growth. Radiation necrosis was seen occasionally in the tumour formations in the lymph glands, but was not common (Figs. 1–4). In a few instances epithelioid cell formations were also found (Fig. 5).

(3) Our most striking finding has been the infrequency of malignant infiltration of the parametrium. In 404 patients with cervical cancer upon whom radical surgery was performed, malignant infiltration of the parametrium was found in only 15 (3·7 per cent), and in 7 of these it had not been suspected at clinical staging (Table II). The incidence of malignant involvement of the parametrium was 3·4 per cent in patients who had received pre-operative irradiation and 4·8 per cent in those who had not. At the same time, among 35 patients who were recorded as of "Stage 2, parametrium", malignant involvement of the parametrium was found in only 2.

These findings are in marked contrast to the 24 per cent incidence of lymph gland metastases.

TABLE II

Cervical Cancer: Proved Parametrial Involvement

(In 15 of 404 patients)

	Patients	Clinical Stage					Irradiation		Negative Glands		Positive Glands		Survival
		One	Two Vagina	Two Parametrium	Two Vagina and Parametrium	Four	Pre-Operative	None	Alive	Dead	Alive	Dead	
1950–54 Total ..	6	1	–	1	3	1	5	1	1	2	1*	2	2
1955–59 Total	9	2	3	1	2	1	6	3	2	2	2	3	4
10 Years	15	3	3	2	5	2	11	4	3	4	2	6	5

* Died in 6 years without cancer.

They are also in accord with our clinical experience that parametrial infiltration due to uterine cancer is much more often inflammatory than neoplastic, and that the clinical staging of parametrial involvement is correspondingly inaccurate. To minimize this error all patients are clinically re-staged under anaesthesia after admission, and again before irradiation or surgery if an intervening period of medical treatment has been necessary. Anaemic and infected patients with parametrial infiltration can often be given a lower clinical staging after adequate bed-rest, blood transfusions, chemotherapy and, when indicated, low dosage deep X-rays. This method has helped to keep to a minimum the incidence and extent of parametrial staging in this series.

Treatment

We believe that in the operative treatment of invasive cervical cancer it is fundamental to remove the pelvic lymph glands, if this can be done with safety. The same applies to many cases of cancer of the uterine body. Our reasons are these:

(i) Lymph glands which contain metastases may appear perfectly normal, as in over 30 per cent of cases in this series.

(ii) Enlarged or adherent carcinomatous glands remaining in the pelvis often cause intractable pain. Safe removal of these glands may prolong life and generally ensures a more tolerable mode of dying.

(iii) Cancer of the uterine body which encroaches on the lower half of the uterus has the same tendency to pelvic gland metastasis that cervical cancer has, and therefore requires lymphadenectomy.

(iv) In our experience adeno-acanthoma of the uterine body has an 18 per cent incidence of lymph gland metastases and also requires lymphadenectomy (Table III).

Table III

Body Carcinoma—Histology, Mortality

No. of Patients	Histology: Type	Histology: Incidence	Negative Glands: Alive	Negative Glands: Dead	Positive Glands: Alive	Positive Glands: Dead	Survival: No.	Survival: Percentage
	1950–54							
20	Adenocarcinoma		18*	2	–	–	18	90
10	Adenoacanthoma		5†	3	2‡	–	7	70
2	Squamous carcinoma	*All*	2	–	–	–	2	100
2	Mesodermal mixed tumour ..	*Patients*	1	1	–	–	1	50
34	*First 5 years*		26	6	2	–	28	82
	1955–59							
42	Adenocarcinoma	67%	31	7	2	2	33	78
12	Adenoacanthoma	24%	10	–	1	1	11	91
2	Squamous carcinoma	4%	1	–	–	1	1	50
2	Mesodermal mixed tumour ..	4%	1	–	1	–	2	100
58	*Second 5 years*		43	7	4	4	47	81
92	*Total 10 years*		67	15	5	5	72	78

* One died 5 months later
† One died 2 years 5 months later } Medical causes.
‡ One died 8 months later, distant metastases.

Present Series

In 415 patients with cancer of the cervix, the operations performed were Wertheim hysterectomy in 375, pelvic exenteration in 29, and lymphadenectomy alone in 11. In 100 of these patients the removed glands contained cancer. Wertheim hysterectomy was also performed on 92 patients with cancer of the uterine body, and in 10 of these the removed glands contained cancer (Table IV). Some details of the operative procedures and results are given in Tables V, VI, VII and VIII.

Table IV

Uterine Cancer: Operations Performed

	Operations	Patients	Positive Glands	
			Number	Percentage
Cervical cancer	Wertheim	375	84	22·4
	Exenteration	29	12	41
	Lymphadenectomy alone	11	4	36
	Total	415	100	24
Body cancer	Wertheim	92	10	11

Table V

Cervical Cancer: Results of Treatment by Wertheim Hysterectomy and Irradiation

Treatment	Number of Patients	Negative Glands		Positive Glands		Percentage Survival		
		Alive	Dead	Alive	Dead	Negative Glands	Positive Glands	All
1950–54								
Surgery only	49	32	9	2	6	78	25	69
With radon	43	26	6	–	11	81	–	60
With radon and deep X-ray therapy	55	35	13	4	3	73	57	71
With deep X-ray therapy	1	–	–	1	–	–	100	100
First 5 years	148	93*	28	7†	20	76·8	26	67·6
1955–59								
Surgery only	31	19	4	7	1	83	87	84
With Radon	105	67	5	25	8	93	76	87
With Radon and deep X-ray therapy	74	50	11	5	8	82	38	74
With deep X-ray therapy	4	1	2	–	1	33	–	25
With megavoltage therapy	13	6	5	2	–	54	100	61
Second 5 years	227	143	27	39	18	84	68	80·2
Total 10 years	375	227	64	46	38	78	54·7	72·8

* Nine dead in next 4 years, 5 from cancer, average time 9 months; 4 medically, average time 2 years 4 months.
† One with pelvic and vulval recurrence at 8 years.

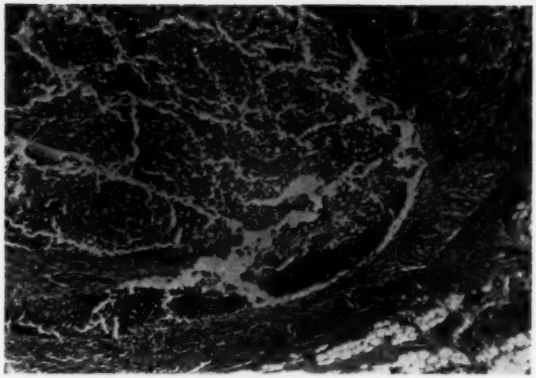

FIG. 1
Lymph node showing large area of necrosis with small rim of surviving carcinomatous tissue. Low magnification.

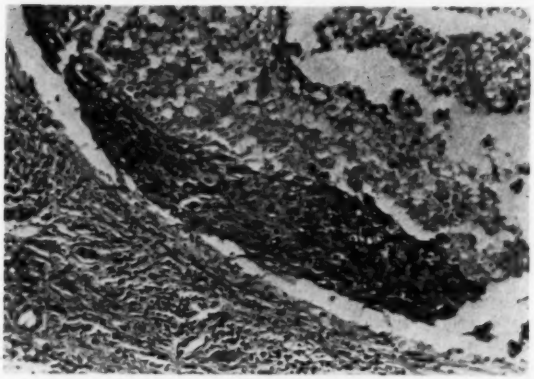

FIG. 2
The same under medium power.

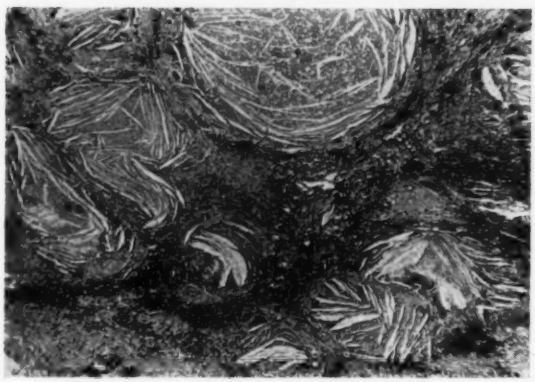

FIG. 3
Multiple areas of necrosis containing many cholesterol crystals with foreign body giant cells, presumably the result of irradiation on metastases.

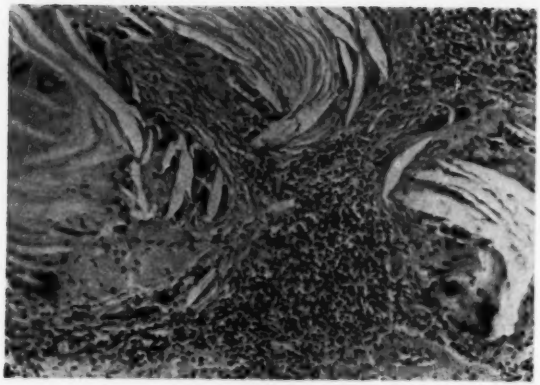

FIG. 4

Details of Fig. 3 under higher magnification.

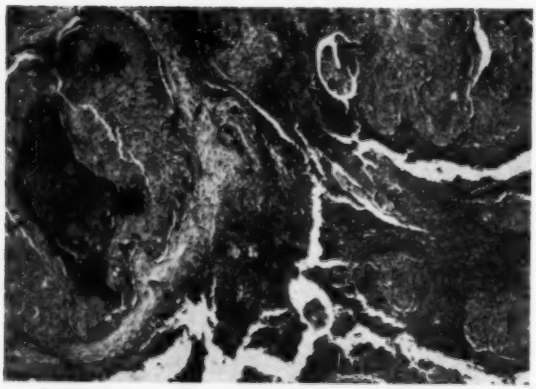

FIG. 5

Sections through a lymph node showing carcinomatous metastases on left side and in the right upper quadrant. Three "tubercles" in the right lower quadrant.

TABLE VI

Cervical Cancer: Wertheim Hysterectomy, Staging

Clinical Stage	Number of Patients	Negative Glands		Positive Glands		Percentage Survival
		Alive	Dead	Alive	Dead	
One	64	48	11	2	3	78
Two	81	45	17	4	15	60
Three	2	–	–	1	1	50
Four	1	–	–	–	1	–
1950–54	148	93*	28	7	20	67·6
One	116	86	5	17	8	88·7
Two	107	56	21	21	9	71·9
Three	4	1	1	1	1	50·0
Four	–	–	–	–	–	–
1955–59	227	143	27	39	18	80·2
Total 10 years ..	375	227	64	46	38	72·8

* Nine dead in next 4 years.

TABLE VII

Cervical Cancer: Pelvic Exenteration

Type of Exenteration	No. of Patients	Negative Glands		Positive Glands		Survival
		Alive	Dead	Alive	Dead	
1950–54						
Anterior	14	1	8	–	5	1
Total	4	–	1	1	2	1*
First 5 years ..	18	1	9	1	7	2 (5 years)
1955–59						
Anterior	10	3	3	2	2	5
Posterior	1	–	–	–	1	–
Second 5 years ..	11	3	3	2	3	5
All, 10 years ..	29	4	12	2	11	6

* Died 6 years without cancer.

TABLE VIII

Cervical Cancer: Pelvic Lymphadenectomy Only

Years	No. of Patients	Negative Glands		Positive Glands		Survival
		Alive	Dead	Alive	Dead	
1950–54	6	1	3	–	2	1
1955–59	5	3	–	1	1	4
Total 10 years ..	11	4	3	1	3	5

TABLE IX

Cervical Cancer: Irradiation and Wertheim Hysterectomy. Malignant Glands

Surgical Method	No. of Patients	Positive Glands	
		Number	Percentage
Wertheim alone	80	16	20
Wertheim with radon	148	44	30
Wertheim with radon and deep X-ray therapy ..	129	20	15·5
Wertheim with deep X-ray therapy	5	2	40
Wertheim with megavoltage therapy	13	2	15·5
Total	375	84	22·4

IRRADIATION

Prior to surgery, radical irradiation was given to 79 per cent of patients with cervical cancer, and to 66 per cent of those with cancer of the uterine body (Table IX). The methods are described below.*

To the surgeon, the chief benefits of irradiation are reduction in the size of the growth and subsidence of infection, and if operation follows in about 6 weeks dissection is easier and there is less bleeding.

After irradiation residual growth was found in the uterus removed at operation in 31 per cent of cases of cervical cancer, and in 30 per cent of cases of cancer of the uterine body.

RESULTS OF TREATMENT

In this series the immediate and remote mortality and morbidity rates have been, in our opinion, a little too high, but they have been contributed to by a number of surgeons during an experimental period.

In the treatment of cervical cancer with metastases in the lymph glands it has been possible to obtain by Wertheim hysterectomy a 5-year survival rate of 26 per cent, which is one-third that of patients whose lymph glands were free of cancer. Of 57 patients who were treated by Wertheim hysterectomy in the last 5 years, two-thirds are still living (Table V).

Of 8 patients treated by pelvic exenteration in the first 5 years, one survived for 6 years to die of an intercurrent disease and without cancer; and of five who were operated on in the last 5 years two are still living (Table VII).

With cancer of the uterine body and lymph gland metastases the outlook is also grave, and of 8 patients operated upon in the last 5 years four have already died (Table III).

I would like to conclude with these observations:

(1) When frankly malignant glands are found in the pelvis at operation it is usually worth while to attempt to remove them. This may be advisable even if the para-aortic glands are also involved; a number of our patients so treated have survived for upwards of 3 years, to end their days without pain or distress.

When malignant glands appear to be inseparably adherent to the great vessels, gentle and painstaking dissection may find a plane of cleavage, for many of these glandular masses have a false capsule. When a mass of glands has enveloped and partly occluded the external iliac vessels, removal of the mass with excision of the vessels will not usually embarrass the vascularity of the limb as a collateral circulation is almost certain to be partly established.

* (1) For cervical cancer, a modified Paris technique was used, with radon instead of radium. A single insertion of 6 days was given to the uterus and upper vagina. In addition deep X-ray therapy was given to the pelvic glands until three years ago.

(2) For body cancer intracavitary irradiation was given to the uterus, and, in the last two years, to the whole of the vagina.

(2) In our experience, particularly in the earlier years, the commonest of the crippling sequelae of radical surgery were those due to damage of the urinary tract, most often the result of extensive clearance of the parametrium. Acquaintance with these complications, and with the infrequency of malignant involvement of the parametrium in this series, makes it evident that clearance to an extent which causes permanent vascular or urinary tract damage is unrealistic and unjustified.

(3) With cancer of the uterine body it is important to know before operation the histological type of the growth, and also whether the lower half of the uterus is involved. This information can be obtained most accurately by fractional curettage.

(4) If our present attitude to the treatment of uterine cancer could be put in a few words, it might be in these terms: "Have no faith in the uterus; have no hope for the lymph glands; but spare a little charity for the parametrium."

Acknowledgments

I am indebted for advice and help to a number of colleagues, in particular to Dr. H. F. Bettinger and Dr. R. A. Barter, pathologists; to Dr. W. P. Holman and Dr. G. R. Kurrle, radiotherapists; to Dr. Kevin McCaul, anaesthetist; and to the late Dr. Graham Godfrey who, for ten years before his untimely death in January 1960, was an outstanding and devoted worker in this field.

DISCUSSION ON THE PATHOLOGY AND TREATMENT OF MALIGNANT GLANDULAR METASTASES OF THE LATERAL PELVIC WALL

Dr. G. W. Blomfield (Sheffield) pointed out that radiotherapy successfully controls or destroys glandular metastases from tumours in other sites in the body and that therefore it should be able to do so in the pelvis. He was, however, against the suggestion that with more powerful machines external radiation alone might be satisfactory, as accurate application could only be made with intracavitary radium. He went on to describe his method in which he used varying sizes of perspex applicators with a tungsten screen for the rectum. Inert radon seeds were used as markers to outline the margins of the tumour on radiological examination. Supplementary therapy with cobalt or 2 million voltage machines was given, the central area which had already been irradiated being shielded by a lead obturator. A dosage of approximately 4,500 r. is delivered to the side wall in Stages I and II, and a somewhat higher dosage in more advanced cases. Results have shown improvement for 5-year survival figures from 21·4 per cent to 31 per cent and now to 41 per cent in each 5-year period during the last fifteen years.

Dr. Joe Meigs (Boston, U.S.A.) gave a brief summary of the reasons which led him to adopt a surgical attack, and illustrated individual variations of radiation resistance and sensitivity by reference to the effects of the atomic bomb in Hiroshima. He was now trying, in co-operation with Dr. Graham, to decide which patients would benefit best from radiation therapy and which from surgery, for he feels that both methods should be used, but not in combination. His cases treated surgically showed a 90 per cent 5-year survival rate, but some of these had required subsequent radiation treatment; of those treated solely by surgery 71 per cent survived 5 years. After 10 years some 70 per cent were still alive, and 24 per cent of these had had growth present in the lymph nodes. He pointed out the importance of removing as much parametrium as possible and said that in giant whole specimen sections it was possible to see growth disseminating along small nerve channels as well as in the lymphatics. The parametrium was very important but the lymph nodes were even more important.

MR. W. MILLS (Birmingham) wished to reinforce what Dr. Hill had said about carcinoma of the corpus uteri and the importance of removing the lateral wall lymph nodes. In the first 12 cases in which he removed the nodes, 6 showed positive nodes but they were advanced cases; now 20 to 25 per cent of his cases showed positive nodes. For the past eight years he had made a practice of routine removal of these nodes and he gave three reasons for this:

(1) There was a small salvage amongst those with positive nodes.
(2) The knowledge of the condition of the nodes was a good index for prognosis and helped the decision for or against post-operative radiotherapy.
(3) It was good palliative treatment in that it prevented pain due to sciatic nerve involvement in those cases which developed recurrences.

PROF. MCCLURE BROWNE (London) thought that it was impossible to remove the lymphatic channels as opposed to the nodes, and illustrated his point with a slide showing the pelvic viscera at operation after injection of vital blue into the cervix. In particular he pointed out the spread of the dye around the lower end of the ureter. He considered that these lymphatic plexuses could not be removed surgically. If the nodes were involved there was no point in removing them surgically; if they were not involved then they did not require removal.

MR. J. STALLWORTHY (Oxford) said that three questions must be asked. First, could lymph nodes on the side wall of the pelvis be treated by radiotherapy? He said there was evidence to show that radiation can destroy tumour cells in lymphatic channels but that evidence about the nodes themselves was less clear. Therefore it might be logical to remove affected lymph nodes and subsequently to treat any remaining tumour cells in lymphatic channels by radiation. Secondly, he asked whether apparently fixed glandular metastases were inoperable? He thought that such metastases could be removed even when the blood vessels were involved. He stated that he disagreed with the use of surgery alone and said there was a case for a combination of surgery and radiotherapy; for example he mentioned a case which had not received pre-operative radium insertion but was found to have positive lymph nodes.

His final question was whether masses on the side wall after surgery or radiation were always due to a recurrence? This was not necessarily so, and he pointed the corollary that recurrence may be present when there is no palpable mass. In two of his cases these masses had been fixed lymphocysts; these were smooth hard swellings adherent to the inside wall, in contradistinction to the soft cystic lymphocysts which occur immediately after Wertheim's hysterectomy.

In conclusion, he pointed out that the overall results for all cases seen are universally bad, as 60 per cent of women succumb to their disease, and he made a strong plea for a combined approach from the radiotherapist and the surgeon.

DR. W. G. COSBIE (in reply) said that his experience with megavoltage therapy was that a definite measured dose can be delivered to the side wall. As a result he sees fewer complications from the treatment; in his view this was the greatest advantage of such therapy. He stated that recurrences can occur up to 20 years after radiotherapy and asked whether these might not be new primary tumours induced by the previous radiotherapy. For carcinoma of the corpus uteri his present method of treatment was to give preliminary radium treatment and follow this in six weeks with a total hysterectomy, bilateral salpingo-oöphorectomy and removal of a cuff of vagina. He had found that if residual cancer was found in the uterus after radium treatment, then the 5-year survival rate diminished to 50–60 per cent; that if invasion of the myometrium by the tumour had occurred, then the overall survival rate was lowered; and, finally, that positive lymph nodes were found above the brim of the pelvis more often than they were in the pelvis.

DR. A. D. CAMPBELL (in reply) pointed out that major surgery is performed by surgeons with varying degrees of skill and that this

vitiates results. He condemned the so-called modified Wertheim's hysterectomy performed by some such surgeons as "adding mutilation to disease". To date, there is no such thing as a cure for cancer.

DR. HILL (in reply) stated that involvement of glands was more important than spread in lymphatics. "Fixed" nodes have a false capsule, which enables them to be removed. In certain cases the nodes can be removed with the involved segment of blood vessels; the blood supply to the leg is satisfactorily maintained by the collateral circulation which has previously developed in such cases. He personally preferred the combined use of radium and surgery. The recurrent masses on the lateral pelvic wall were most often infective in his experience and also the commonest involvement of the parametrium was inflammatory, and this tended to vitiate the accuracy of staging. Only 42 per cent of his cases of carcinoma of the body of the uterus undergo Wertheim's operation, but all cases are preceded by intracavitary radium and a surface dose to the vagina.

THE USE AND ABUSE OF ANTIBIOTICS

BY

RONALD HARE, M.D.
Professor of Bacteriology
University of London

IT is perhaps appropriate that one of the scientific sessions that mark the opening of this new college should be devoted to a discussion on antibiotics. For I need hardly remind you that it was largely due to the investigations carried out in an obstetric hospital by an honorary Fellow of this College, Dr. Colebrook, that the real possibilities of modern chemotherapy first emerged; and although the work I refer to—which showed that women need not die of puerperal fever—concerned sulphonamides, I doubt very much whether penicillin and succeeding antibiotics would have emerged from their former obscurity had it not been for the fact that the sulphonamides clearly demonstrated what could be achieved in combating bacterial infection.

Since that time, modern chemotherapy has developed so rapidly that in addition to puerperal fever and other streptococcal infections we can now cure a host of different diseases and of such diverse aetiology and pathology as syphilis, meningitis and typhus.

Nevertheless, quite apart from the undesirable effects that may accompany treatment with almost any drug and from which antibiotics are by no means exempt, these chemotherapeutic agents have three fundamental disadvantages not possessed by almost any other form of treatment.

The first of these disadvantages is that even though they may be highly susceptible when they first encounter an antibiotic, certain species of micro-organisms can, almost certainly as a result of mutation and natural selection, become resistant. This resistance then becomes a more or less permanent characteristic. Ability to become resistant depends to a great extent on the species of organisms involved and the antibiotic to which it is exposed, but the tubercle bacillus and the staphylococcus are the most gifted in this respect, whereas other micro-organisms such as the streptococcus show much less tendency to become resistant.

The second disadvantage of an antibiotic is that it must necessarily act on aetiological agents that to a greater or lesser extent can escape from its influence while the patient is under treatment. For whether organisms are sensitive or resistant they are generally able in one way or another to travel to other persons in the community by the process we nowadays refer to as cross infection. This means that if a strain of a particular micro-organism becomes resistant while producing infection, the resistant survivors may, indeed frequently do, become disseminated to other individuals who either become carriers or suffer from infection in their turn. Thus the emergence of a resistant strain must not be looked upon as merely an unfortunate accident but as something that concerns the community as a whole.

Although any organism that can become resistant may behave in this way, *Staphylococcus aureus* is by far the most important. This was demonstrated as long ago as 1947 when penicillin-resistant strains were first detected. In consequence of this, penicillin began to lose its value for the treatment of some infections. The expedient employed to get over this difficulty was to use another antibiotic which at that time was streptomycin. But staphylococci became resistant to this antibiotic even more readily than they do to penicillin, and still other antibiotics had, therefore, to be brought into use. None of them defeated the staphylococcus which has

been able to keep ahead of pharmacological progress by becoming resistant to each new antibiotic that has been introduced. Until recently we have been able to keep the situation under partial control because new antibiotics have generally appeared in time. But we are now face to face with the third disadvantage of antibiotics. That despite the multiplicity of names given to them, there are in fact very few antibiotics. Indeed not more than about a dozen all told.

This paucity is due, fundamentally, to the fact that antibiotics come from moulds, and it is only the very exceptional mould that can produce a useful antibiotic at all. Indeed tens of thousands of moulds must have been examined to find the 12 which produce antibiotics that are of value. It is, therefore, wishful thinking to assume that many more antibiotics are likely to become available from naturally occurring moulds in future years. Nor are we entitled to assume too readily that the chemists will come to the rescue and evolve new antibiotics in the test tube for use in the immediate future.

Thus we are faced with a situation that is, as far as I know, completely new to medicine. That with a very limited number of therapeutic substances available, we are trying to combat aetiological agents that can escape from our therapeutic control by not only becoming resistant to each substance as soon as they encounter it, but by becoming disseminated far and wide in the community.

Because of this the treatment of infections by antibiotics is by no means so simple as are many other forms of treatment. For it necessitates not only treatment of the infection itself, but an awareness on the part of the physician of the consequences both to the patient he is treating, and to possibly innumerable patients in the future, if the infecting organisms become resistant. The particular techniques the physician can employ to prevent the emergence of resistant strains and to control them if they do, will, I have no doubt, be referred to by subsequent speakers. But to my mind, the most important aspect of all, is that the phycisian must realize every time he uses an antibiotic that powerful weapon though it may be, the organisms it is called upon to combat can, unless carefully controlled, react so violently and successfully that the antibiotic may soon become useless.

It is for this reason that we are met here today to discuss the uses and abuses of antibiotics.

THE USE AND ABUSE OF ANTIBIOTICS—*continued:*

DRUG-RESISTANT STAPHYLOCOCCAL INFECTION

BY

MARY BARBER, M.D.

Postgraduate Medical School of London

ABOUT 25 years ago, prontosil was first used in the treatment of puerperal sepsis (Colebrook and Kenny, 1936). It is perhaps difficult for young obstetricians today to appreciate the drama of this. But, prior to the introduction of the sulphonamides, if a patient became infected with a haemolytic streptococcus in the puerperium she was expected to die, and the curative effect of prontosil was, in the words of Colebrook (1956), "something we had never seen in ten years experience of the disease".

Today, I shall speak mainly about one of the unfortunate effects of the use, or perhaps I should say, misuse, of sulphonamides and antibiotics, namely, drug-resistant staphylococcal infection. But, in order to put this in true perspective, I wish first to draw attention to the remarkable fall in the incidence and mortality of infections since 1935. Although it cannot be claimed that antibiotics are solely responsible for this, it is certain that they have played a major part.

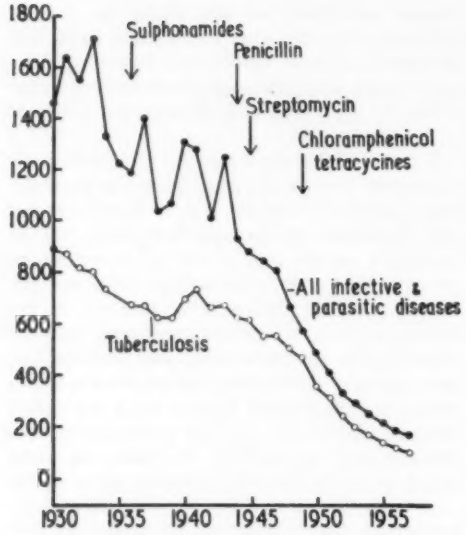

FIG. 1

Deaths from all infective and parasitic diseases per million living in England and Wales, 1930 to 1957.

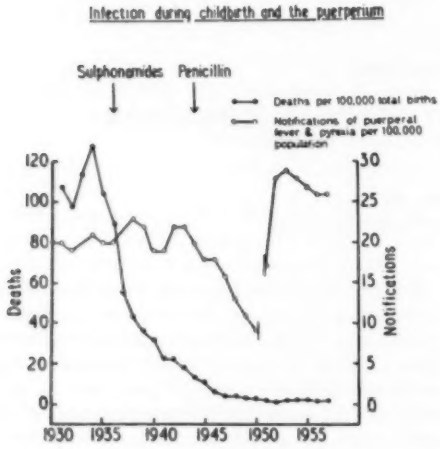

FIG. 2

Puerperal pyrexia. Deaths per 100,000 total births and incidence per 100,000 population in England and Wales, 1930 to 1957.

Figure 1 shows the number of deaths per million living in England and Wales from all forms of infectious disease, between 1930 and 1957. It will be seen that since the introduction of antibiotics the mortality from infectious diseases has fallen by more than 80 per cent. It is of interest to note that in 1934 the number of deaths from infection was ten times the number of deaths on the road. By 1957 the figures were almost equal, although deaths on the road in that year were no higher than in 1934.

Figure 2 shows the deaths from puerperal infection per 100,000 total births in England and Wales for the same period. It will be seen that deaths from this condition have fallen to a very low level indeed since the introduction of sulphonamides. The incidence of puerperal pyrexia per 100,000 population is also shown and it will be seen that after an initial fall, there was apparently a sharp increase in 1951. It will not be necessary for me to explain to this audience that the increase reflects a change in the definition of puerperal pyrexia for the purposes of notification, rather than a true increase in the incidence of infection.

EMERGENCE OF DRUG-RESISTANT STAPHYLOCOCCAL INFECTION IN HOSPITALS

Not all bacteria, however, have taken the attack lying down, and certain species, notably *Staph. aureus*, *Myco. tuberculosis* and coliform bacilli, have shown a quite remarkable capacity to adapt themselves to the presence of antibiotics. With the staphylococcus, indeed, there has been a neck and neck race between the discovery of new anti-staphylococcal agents and the capacity of the staphylococcus to breed strains resistant to previous ones.

A rapid and progressive increase in the incidence of drug-resistant staphylococcal infection has been reported from hospitals all over the world in the last ten years or so. Figures 3 to 6 give examples from London, Paris, Sydney and Washington. It will be seen that by 1951 or earlier, the incidence of staphylococcal infection resistant to penicillin was over 50 per cent in all four hospitals. Since the tetracycline antibiotics were not introduced until after this had happened

it was penicillin-resistant staphylococci that became resistant to these antibiotics, so that hospital staphylococci tended to be resistant to both penicillin and the tetracyclines.

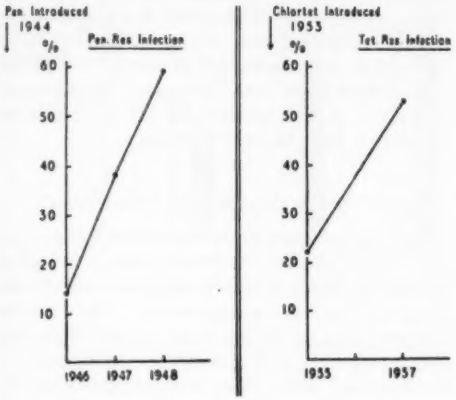

FIG. 3

Increasing incidence of staphylococcal infection in a London hospital resistant to penicillin, 1946 to 1948 (from Barber and Rozwadowska-Dowzenko, 1948) and tetracycline, 1955 to 1957.

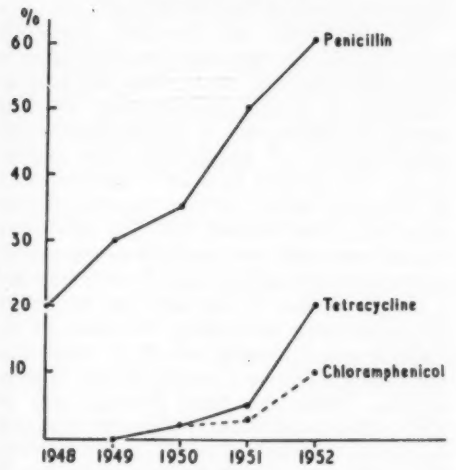

FIG. 4

Increasing incidence of drug-resistant staphylococcal infection among out-patients attending a hospital in Paris, 1948 to 1952 (based on the figures published by Chabbert, Terrial and Schutzenberger, 1953).

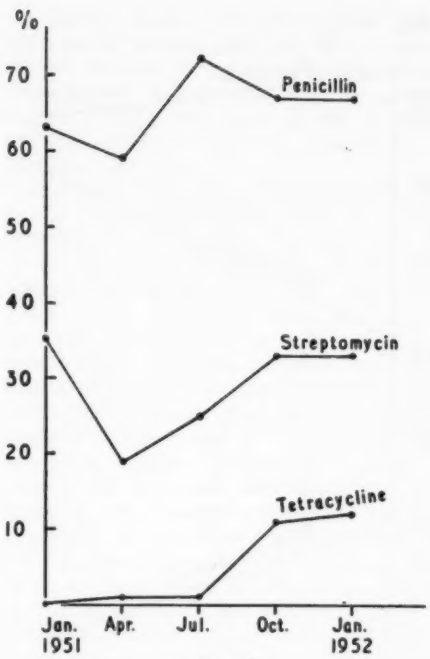

FIG. 5

Increasing incidence of drug-resistant staphylococcal infection in a hospital in Sydney, Australia, 1951 to 1952 (based on the figures published by Rountree and Thomson, 1952).

The situation with regard to streptomycin and chloramphenicol, which were introduced in 1944 and 1948 respectively, is rather different, since neither have been used extensively in general hospitals. Streptomycin has been reserved for the treatment of tuberculosis or acute infections for which there is no other equally effective drug, owing to the rapidity with which most bacteria can become resistant to it. In spite of this restriction, in many hospitals the prevalent staphylococcus is resistant to this antibiotic, as well as to penicillin and the tetracyclines.

The use of chloramphenicol has been kept low because of its possible effect on the bone marrow. This has meant that in most hospitals chloramphenicol-resistant staphylococci are rare. It will be seen from Fig. 6 that in a hospital in Seattle,

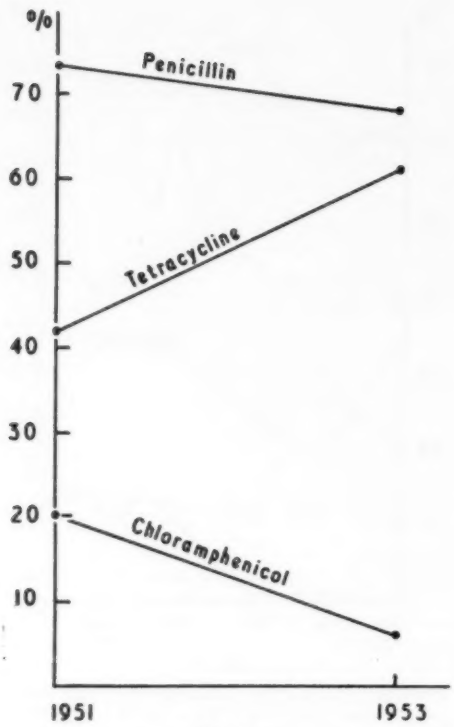

FIG. 6

Increasing incidence of drug-resistant staphylococcal infection in a hospital in Seattle, Washington, 1951 to 1953 (based on the figures published by Kirby and Ahern, 1953).

Washington, the incidence of chloramphenicol-resistant staphylococcal infection fell from 20 per cent to 6 per cent between August 1951 and April 1953, and this was associated with a drastic reduction in the use of the antibiotic, following reports of bone marrow damage.

By the time erythromycin arrived on the scenes, the warning had been sounded, and in most hospitals this antibiotic has been kept in reserve for infections resistant to other drugs. Even so erythromycin-resistant staphylococcal infection is not uncommon, since staphylococci develop resistance to erythromycin so rapidly that a gross change may occur during the treatment of a single case.

Epidemiological studies, including bacteriophage typing of strains, have shown that the rapid increase in the incidence of drug-resistant staphylococci in hospitals is the result of two factors, namely, the extensive use of antibiotics and cross-infection. Thus in the first place, nearly all the drug-resistant strains emerging in a hospital or department are of one or two phage types, which have been "passaged" from patient to patient in the presence of the antibiotic to which they have become resistant.

INFECTION IN MATERNITY DEPARTMENTS

Maternity departments are no exception and, even where there is no gross sepsis, the babies usually go home carrying drug-resistant *Staph. pyogenes* in the nasopharynx. The strains isolated tend to be resistant to penicillin only and are frequently of phage type 52A (Group 1). In this they differ from those responsible for most cases of surgical cross infection, which are usually multiple resistant strains of phage group III or type 80 (Barber and Burston, 1955; Shooter *et al.*, 1958). The maternity strains, however, frequently resemble those carried by a large proportion of the nursing staff.

Examples from two maternity units will illustrate this. The first study was undertaken in a maternity hospital where there had been an outbreak of severe staphylococcal infection among the babies, due to a penicillin-resistant staphylococcus of phage type 52A. Similar strains were isolated from the conjunctiva of 16 of 35 healthy babies and from the noses of more than half of the nursing staff. The latter were studied repeatedly over an eight-month period, and it was found that the nasal carriage remained constant, in spite of the fact that the nurses themselves were continually changing, as the hospital was a training school for pupil midwives who came for a period of one to three months. When the nasal carriage rate of penicillin-resistant *Staph. pyogenes* was studied in relation to the length of time the nurses had been in the hospital, it was found, as shown in Fig. 7, that the two went closely together. Thus only 24 per cent of nurses who had been in the hospital for a fortnight or less carried such strains, whereas the incidence among nurses who had

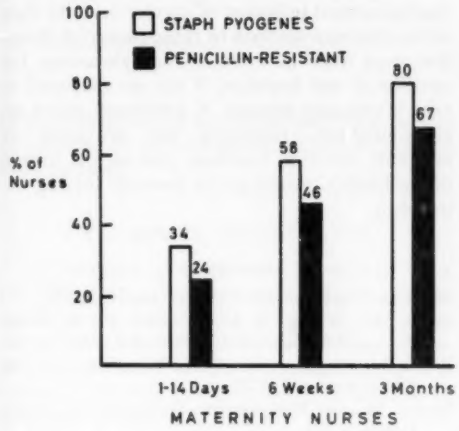

FIG. 7

Nasal carrier state among nurses at a maternity hospital related to time since entry to the hospital.

been there three months or more was 67 per cent. The majority of all typeable penicillin-resistant strains belonged to phage type 52A, so that it is fairly clear that most of the pupil midwives were picking up the prevalent hospital staphylococcus after their arrival (Barber, Hayhoe and Whitehead, 1949).

The second study was carried out in a maternity unit where the sepsis rate was extremely low and such lesions as occurred were trivial. Nevertheless it will be seen from Fig. 8 that 61 per cent of the nurses and 65 per cent of

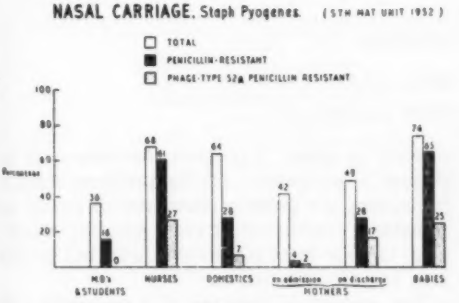

FIG. 8

Nasal carrier state of staff and patients in a maternity department, where there was no gross sepsis.

the babies carried penicillin-resistant *Staph. pyogenes* in the nose, and that about a quarter of the mothers picked up penicillin-resistant staphylococci during their stay in hospital. Again, a large proportion of the penicillin-resistant strains belonged to phage type 52A (Barber *et al.*, 1953).

Thus penicillin-resistant staphylococci appear to be freely disseminated even in a clean maternity unit. To what extent this means that we are sitting on a volcano it is difficult to say. There is some evidence to suggest that carrier strains, in the absence of sepsis, lose some of their virulence. An increase in the incidence of minor sepsis is probably a danger signal. Thus both Rountree and Freeman (1955) and Beaven and Burry (1956) describe outbreaks of severe neonatal infection due to strains which had apparently become of increased virulence by passage among babies suffering from minor infections, the incidence of which had been increasing. In both these studies, however, the infecting staphylococcus was a multiple resistant strain of phage group III (Beaven and Burry) or type 80 (Rountree and Freeman) similar to those occurring in surgical wards, and there is some evidence to suggest that such strains are of higher virulence than those resistant to penicillin only and of phage type 52A (Shooter *et al.*, 1958; Barber *et al.*, 1960).

PREVENTIVE MEASURES

The question remains, what can be done to improve the situation? Since both cross-infection and the widespread use of antibiotics have played their part in the emergence of drug-resistant staphylococcal infection, both must be attended to. In this short communication, it is not possible even to outline measures for dealing with cross-infection, nor to obstetricians should this be necessary. But in view of the work referred to above, it is worth emphasizing that even minor neonatal sepsis should be taken seriously, that there should be as little contact as possible between maternity and surgical wards, and that nurses or doctors carrying multiple resistant staphylococci in the nose should be kept out of maternity units until their carrier state has been changed.

Finally, is it possible by a controlled antibiotic policy to reverse the drug-resistance of hospital staphylococci? A policy involving drastic restriction in the use of penicillin and the treatment of all infections with two drugs in combination has been carried out for two years at Hammersmith Hospital (*see* Barber *et al.*, 1960). During the investigation, more than 5,000 patients were admitted to the surgical wards of the hospital and about 10 per cent were infected with staphylococci, occasionally before, but usually after admission to the hospital. At the beginning of the experiment only 12 per cent of the infections were sensitive to all antibiotics including penicillin; today the figure has risen to more than 50 per cent. During the same period the proportion of strains resistant to penicillin and the tetracyclines has been reduced from 70 per cent to 29 per cent.

That this experiment has not just been an academic exercise is shown by the fact that the mortality from staphylococcal sepsis fell steadily with the fall in the incidence of multiple-resistant infection and that, in fact, of 132 patients with penicillin-sensitive infections only 1, a man 80 years old, died, whereas there were 23 deaths among 224 patients infected with multiple resistant strains.

Conclusion

Today we reap the rewards of the indiscriminate use of antibiotics, in a problem of hospital staphylococcal infection of greater severity than before the introduction of these powerful drugs. But, even with the versatile staphylococcus, the position is not hopeless, if we are prepared to take it seriously enough. A combined attack on cross-infection, including the provision of adequate isolation facilities, and on the misuse of antibiotics, would go far towards solving the problem.

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THE USE AND ABUSE OF ANTIBIOTICS—*continued:*

B. W. Lacey, B.Sc., M.D.

Westminster Hospital, London

Dr. Barber has just emphasized the interdependence of antibiotic usage and cross-infection and the urgent need to control both if infection in the maternity unit is to be reduced to an acceptable minimum. It seems to me that this problem resembles that of cancer, and indeed many others in medicine, in that although many factors are known their relative importance and causal relationships are very difficult to assess. I propose therefore only to present a perspective of the problem from a bacteriologist's point of view, not of course as something established or even generally acceptable, because there is no such thing, but largely as a basis for discussion.

The amount of infection in a maternity unit can conveniently be regarded as the product of the following:

$$\text{Amount of infection} = \frac{\text{Number of organisms transferred to a susceptible site} \times \text{Pathogenicity of the strain} \times \text{Number and susceptibility of the sites}}{\text{Efficiency of chemotherapy}}$$

so that reduction in any of the top three factors or increase in the bottom factor will reduce the total amount.

Transfer of Staphylococci

The number of organisms transferred to a susceptible site in a given time will depend on the nature of the person from whom they arise, the nature of the contaminated site on this person and the efficiency of this person's asepsis. The relative importance of each of these is liable to vary enormously and different observers tend, perhaps at times for emotional reasons, to emphasize one at the expense of another.

My own view of their relative importance in general is represented in Table I.

The almost essential role of infected babies as precursors of breast abscesses and their importance as reservoirs of infection need no emphasis. Nor need one stress the obvious danger of mothers handling other persons' babies. But among the staff it really does seem fair to regard the most junior maternity nurse as the most dangerous. She it is who is most harassed, least experienced in efficient asepsis and most likely to be suffering from a fresh clinical lesion or, usually much more dangerously because so easily overlooked, unconsciously harbouring a lesion of the "second order". At times this is in the form of a hang nail, abrasion of the skin or furuncle of the anterior nares following the removal of a hair, but probably most often as an axillary infection, precipitated by inexpert shaving and often perpetuated by inadequate chemotherapy that is by no means always self-administered. In this respect I believe more good may follow advice from the medical officer to the midwife staff on how best to prevent axillary or nasal infection, by the use of electric shavers, spirit and so forth, than any other single measure. Once axillary infection is established it should be clearly regarded just as seriously as would a whitlow, and a course of autogenous vaccine with toxoid is then probably often the quickest as well as the surest way of getting her back on duty.

It may appear strange to see the nose of babies in a different category to that of adult noses, but it is reasonably certain that the naso-pharyngeal

Table I

Numbers of Organisms Transferred

Relative Importance	Reservoir	Source	Asepsis
■	Junior staff Babies in nurseries Mobile mothers	Lesions	Hands
▣	Senior staff Immobile mothers	Healing lesions Sub-clinical lesions Noses of babies Intestinal tract of mothers on chemotherapy	Clothes Bedclothes Bath scum
□	Visitors Cleaners	Nose and skin of adults Bedclothes Clothes	Nose
□	Isolated mothers and babies	Dust Air	Air

flora of the newborn remains a hot bed for staphylococcal multiplication until the adult flora becomes fully established between the third and sixth month. The relative importance of the sources is by no means exaggerated in the diagrams, for a finger touch from a lesion may transfer 10^8, i.e., a hundred million organisms, whereas from the next class only 100,000, from the third between 100 and 1,000 and from the last less than ten.

In asepsis the emphasis should, in my view, be in the order listed, with the nurses' or midwife's nose well down the list. There is ample evidence that the noses of both staff and patients tend to become colonized from the environment and in general serve as an index of environmental dissemination of a particular strain, but I can find no good evidence that staphylococcal cross infection ever stems directly from an adult nose, or that the use of a mask or any form of anti-nose treatment has by itself been of any value in this respect.

Pathogenicity

There is very little one can usefully say about the pathogenicity of different strains. Other things being equal, the more drug-resistant a strain is the more effectively pathogenic it is liable to be. But although phage type 80/81 strains are well known as ones most to be feared they are by no means the only dangerous ones, and it now seems highly desirable if not obligatory to:

(*a*) Reduce the chances of introducing fresh hospital strains, whose virulence has been exalted by rapid passage in patients, by reducing to a minimum the contact between maternity and surgical staffs.

(*b*) Maintain a continuous appraisal of the situation by

(*i*) bacteriological examination of all wounds, infected sites or sites believed to be infected.

(*ii*) preservation of all cultures in the laboratory.

(*iii*) recording all information in the ward case book.

(*iv*) periodic surveys of nose and skin carriage of staphylococci in patients and staff.

(*v*) continuous follow-up of mothers and infants for six weeks after leaving hospital.

Susceptibility

The fate of pathogenic organisms transferred to new sites is largely a reflection of their ability to multiply rapidly at the new site. (Table II.)

Table II

Factors Affecting Susceptibility

Relative Importance	Baby		Mother	
	Site		Breast	Pelvis
	Umbilicus Nose and throat	First day	(Infection of baby)	Trauma Blood loss Duration
☐	Eye Skin	Second day	Postnatal care with infected baby	Specific immunity
☐		After second day	Antenatal care	

In the newborn child the umbilical wound probably offers the most favourable environment even though its susceptibility falls rapidly with healing. The nose and throat are comparably susceptible and normally show a similar change with age as an immediate result of the colonizable area becoming pre-empted by other organisms from the environment. Colonization of the umbilicus and skin by pathogenic staphylococci is fairly readily prevented by the use of sterile clothes, sterile bath, soap and bath water containing hexachlorophene, chlorhexidine powder and an occlusive dressing. Colonization of the nose, however, is inevitable sooner or later and demands a deliberate policy. One rational way is to keep the nose completely free of staphylococci while in hospital; and Elek has shown that this can be achieved, albeit at considerable cost and perhaps some ultimate risk of sensitization or selection of resistant organisms or both, if sufficient antibiotic BRL 1241* is sprayed daily into the air of the unit. A second way is to promote rapid colonization by the maternal flora. This is clearly best effected by keeping mother and child in isolation although, as we have found at Westminster, a fair second best can be achieved by putting the baby with its mother virtually as soon as it is born, immediately after first bathing, and keeping it there as long as possible. But in my view the most logical method, and the one which will ultimately prove the best of all, is deliberately to swab the nasopharynx of the newborn with a mixed innocuous flora.

* Beecham Research Laboratories, Ltd.

Chemotherapy

To complete this survey I would need much time to discuss the essentials of good chemotherapy; without this I can only present in a bald list a few precepts of strategy and tactics that seem to me of special importance in the maternity unit:

Strategy

Knowledge of sensitivities of strains in the environment.

Minimal prophylaxis.

Early recognition of need for treatment by routine screening for amniotic infection (by gastric smear, chorionic imprint, etc.) and watch for neonatal septicaemia (making early blood cultures) in all cases of prematurity or when infection appears otherwise likely.

Judicious use of combined therapy.

Tactics

Minimal delegation to juniors.
Minimal use of steroids.
Isolation of all treated.
Adequate dosage.
Review in every case on second or third day.

THE USE AND ABUSE OF ANTIBIOTICS—*continued:*

T. F. Corkill, *M.C.*, M.D., Ch.B., F.R.C.P.(Edin.), F.R.C.O.G.
Wellington, New Zealand

It is clear that the advent of these life-saving drugs has introduced a world-wide problem of acquired bacterial resistance against antibiotics, particularly on the part of the *Staphylococcus aureus*.

The practical questions that arise are:

(1) How much of this is inevitable under present circumstances even when these drugs are used in the most legitimate and careful way?

(2) What steps can be taken to limit this "inevitable" occurrence of bacterial resistance to a minimum?

(3) To what extent has the problem been aggravated by the abuse of these drugs?

(4) What are the most serious results of this new development as far as obstetrics and gynaecological practice is concerned?

(5) What steps must be taken to counter these special problems?

The following answers may be given to these questions:

(1) It must, I think, be accepted that, so wide is the legitimate sphere of usefulness of these drugs, unless and until some specific method of preventing the development of such resistance is discovered, it is bound to occur to some degree.

(2) To limit this resistance to a minimum without restricting any legitimate use, two things have become clear. Prophylactic use of antibiotics should be limited to cases where there is real suspicion of exposure to infection. In our particular field it has, for instance, been found advisable to look again at their use for cases with ruptured membranes.

As far as possible, all treatment should be guided by sensitivity tests to avoid adding the effects of useless drugs to the environmental pool.

(3) The third question relates to abuse. That there is an extravagant and quite unnecessary use in some quarters seems to be perfectly clear. Some of our clinicians in New Zealand who have, during travel, observed closely the practice in other countries, have gained the impression that the degree of this abuse is not so great with us as with some.

It should be explained that under our universal health scheme the range of drugs available "free on the Fund" to all patients is very wide. There is, however, always a certain lag before new drugs are placed on the free list and, even when accepted, the Health Department, guided by a Pharmacological and Therapeutics sub-committee on which senior practising members of the profession are fully represented, exercises some control over their issue.

This restriction has undoubtedly limited abuse. Nevertheless, the varying pattern of antibiotic prescribing in different parts of New Zealand strongly suggests some extravagance somewhere. Taking two metropolitan areas, the prescriptions for broad spectrum antibiotics per 1,000 of the population during the last 4 years in one of them averaged 100 per cent more than in the other. But the possibilities of abuse are not limited to such examples of extravagant prescribing by private practitioners. We are all aware that, until recently at least, penicillin and other antibiotics were given in some hospitals on very slender indications. There can be little doubt that such extravagance aggravated the resistance problem.

(4) The most serious results of this widespread resistance to antibiotics as far as obstetrical practice is concerned are the very great increase in maternal breast infections which has been the general experience, and the similar considerable increase in minor neonatal infections with the occasional occurrence of outbreaks of more serious and fatal pulmonary infection. For example, in New Zealand in 1950, among 69,000 admissions to our public hospitals, there were 132 cases of breast abscess. In 1957 there were 708 cases in 84,900 admissions. In our two Wellington hospitals there were 13 cases in 1950 and 53 in 1958.

Many investigations have shown the possible danger point in the maternity hospital nursery, starting it is believed with a member of the staff, nursing in particular, who is a carrier of a penicillin-resistant staphylococcus of particularly virulent phage type as the result of an unrevealed present lesion or a recent episode of infection by such an organism. Infection of a baby may be by droplet infection from such a carrier or by touch. Airborne transmission from one such baby to another may occur. It is not unlikely that infected dust or blankets may further contribute to the spread.

There is general agreement that maternal breast infection is almost always derived from the infant during nursing. Not only has the incidence of breast abscess greatly increased for these reasons, but the development of penicillin resistance in particular has complicated treatment; whereas 10 years ago penicillin was confidently regarded as highly successful in aborting mastitis, today it is so frequently ineffective that other antibiotics must be the first choice.

Although the desperate case of infection resistant to practically all the commoner antibiotics is rare in obstetrics, it must be the occasional experience both here and in gynaecological practice. For that reason we cannot but agree with the restriction of one of the more

recently introduced potent antibiotics to meet such emergencies.

(5) What steps must be taken to counter these special problems of maternity practice? One very serious question in New Zealand is whether the modern well-equipped maternity hospital nursery unit which undoubtedly did much to reduce neonatal mortality, including that due to infection as it was met with until recent years, must now be abolished and superseded by a system of rooming-in because of the present challenge. Such a change will require the complete alteration of many existing maternity hospitals because, in my opinion at least, rooming-in simply cannot be adapted effectively to the multiple-bed wards of many of today's hospitals. It has already entailed very great additional expense in some hospitals now under construction through change of plans.

If we are to adopt this principle of rooming-in on grounds of cross-infection danger, it must be complete. It will mean the provision of a large proportion of single rooms or wards of not more than 2 to 4 beds very specially adapted. This, indeed, is advocated for other reasons as well. Undoubtedly, rooming-in under such properly prepared conditions could help to a considerable extent with this particular problem, but the loss of the carefully supervised nursery with some trained staff always on duty will introduce some disadvantages and even some risks that seem to be forgotten.

Once a compromise develops and a small nursery is included to which the crying baby, for instance, can be retired at night, complications will arise. And where will it stop? I can foresee overcrowding of this small nursery rapidly developing.

Some provision will also have to be made for the baby requiring twenty-four hours initial rest or the not inconsiderable number of babies calling for other special care. Is this the nursery to which the crying rooming-in baby will be banished at night or will there be another?

Will nursing contacts with the babies be greatly reduced? Will the first nursing care of the rooming-in baby—including cord attention and napkin-changing be left entirely to the early puerperal mother?

We have learnt that probably the most dangerous carrier is a nurse with an unsuspected recent lesion. How will such a nurse be eliminated from attendance on several rooming-in babies with possible further extension of infection if transfer to a night nursery occurs?

Is there no other way of meeting the challenge? Thirty years ago the maternity hospital was similarly regarded by many as a potential risk both to mother and baby by reason of the dominant streptococcal infection danger of that time. In New Zealand we met that problem by meticulous attention to the details of an aseptic and antiseptic technique. Those were the days when we endeavoured in the teaching of nurses to develop the "aseptic concience" which instinctively recognized the slightest slip. The result was that between 1927 and 1936, before the advent of sulphonamides even, deaths from sepsis following childbirth fell from 2·1 to less than 0·36 per 1,000.

It is my belief that that basic, deeply ingrained understanding of the practice of asepsis is not as fully appreciated today. Antibiotics and more potent antiseptics have brought over-confidence. The prolonged hand preparation of earlier days is criticized and scoffed at; a cursory wash and a so-called no-touch technique is more the fashion. The isolation unit once again becomes an important feature of a maternity hospital to meet this different hazard.

Finally, it is our hope that the control of the development of bacterial resistance itself will, in the course of time, become possible. The work of Dr. M. Barber and her associates (1960) on the reversal of resistance is encouraging, and more recently one has been greatly impressed with the clinical experiments of Professor S. D. Elek and Dr. P. C. Fleming (1960), at St. George's Hospital in which, with a new experimental antibiotic (AB, 1241) used as a room spray, they were able to eliminate the nasal carriage of *Staphylococcus pyogenes* by the babies in a maternity ward and nursery. The possible development of this approach will be watched with great interest.

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DISCUSSION ON THE USE AND ABUSE OF ANTIBIOTICS

MR. BRYAN WILLIAMS (Middlesbrough) in, an amusing and somewhat allegorical discourse, gave a warning against what he called the "antibiotic lotus land", and appealed for a return to the basic principles of antisepsis. He felt that the high bed occupancy encouraged by the Ministry of Health led to over-crowding and was a factor in the problem of sepsis.

MR. A. C. H. BELL (London) referred to an outbreak of breast abscess caused by *Staphylococcus aureus* phage type 80, which had occurred at his hospital. A large number of babies had been found to have the organism in their mouths within three days of birth. As it had been shown that such colonization was only likely in the absence of the ordinary bacterial flora the babies had been put to the mothers' breasts in the labour ward soon after delivery. To eradicate the organism from the wards many measures had been adopted, of which the following were enumerated: the use of cotton cellular blankets, of plastic mattress covers, of incinerators on the ward for the disposal of soiled material, of hexachlorophene soap for hand-washing, of hexachlorophene spirit to clean baths and of vacuum cleaners with special filters for ward cleaning. There was minimal usage of antibiotics and this only when patients were isolated. As a result of all these measures the problem appeared to have been solved to date, as he could remember no further cases developing.

DR. D. STANDING (Durban) said he was surprised that no mention had been made of monilial infections occurring as a side-effect of antibiotic therapy. This was a very common condition in South Africa and he estimated that 3 out of every 10 women in the population had monilia present in the vagina. Infection of the bowel was also very common and was difficult to treat. He described a case where bowel infection with monilia had occurred subsequently to antibiotic therapy, and in which death resulted from multiple intestinal haemorrhages. On microscopical examination all the capillaries and small blood vessels were filled with monilial hyphae and spores.

DR. ARTHUR HILL stated that in Melbourne the problem of staphylococcal infection became much worse in 1956. There was then no controlled use of antibiotics; terramycin was being frequently given and the paediatricians were prescribing terramycin prophylactically. The problem was faced by forming a Control of Infection Sub-committee and adopting a policy of using only one antibiotic for a period of six months at a time, starting with erythromycin, and continuing with gleandomycin and chloramphenicol. Cannamycin followed, and it was possible to use this drug for nine months before returning to terramycin once more. Now only about 10 per cent of strains were found to be insensitive. At the end of last year the Department of Pathology of the University of Melbourne had investigated the incidence of staphylococci amongst patients in three different types of hospital, a General Hospital, The Women's Hospital and a Mental Hospital. The results were as follows:

Nasal Carrier Rate (Staph. pyogenes) *for In-patients* (percentages)

General Hospital	54
Royal Women's Hospital	36
Mental Hospital	36

Percentage of Staphylococci Showing High Antibiotic Resistance

	From Nose	*From Bedclothes*
General Hospital ..	63	40
Royal Women's Hospital	17	11
Mental Hospital ..	6	0

These figures illustrate, in three different types of hospital, the results of three different types of antibiotic usage: uncontrolled use, controlled use, and little or no use.

Under the controlled scheme described there was no restriction of the use of penicillin and sulphonamides. The decision over antibiotic

therapy was not to be delegated to junior staff but must be the responsibility of the consultant staff. With reference to hexachlorophene soap, the speaker said that this had to be used regularly over a long period of time to achieve the best results.

PROF. MCCLURE-BROWN (London) described a heroic performance of William Smellie over an internal version and pointed the lesson of the strong recuperative powers of the patient. He gave a warning against the present preoccupation with natural childbirth and the attempt to make hospitals more like the home being allowed to interfere with proper anti-infective precautions. Antibiotics could be dangerous drugs and he mentioned two cases where death had resulted from their use for trivial complaints. He said that he always used two antibiotic drugs simultaneously, and stressed the need for careful attention to asepsis and a return to the principles of the pre-antibiotic era.

DR. SOPHIAN (London) stated that the risk of infection following amniotomy, a point made by Mr. Bryan Williams, was in fact very small. He mentioned that he had had several cases of monilial enteritis, some of which had entered a very chronic phase and asked if nystatin was capable of controlling this type of infection.

PROF. IAN DONALD (Glasgow) said that antibiotics should only be prescribed on the authority of a consultant. He made a plea that babies should be handled in the main by their mothers, and he heartily condemned the practice of bathing the babies, saying that it was unnecessary, and bacteriologically speaking it was a dirty habit.

MR. J. A. CHALMERS (Worcester) made three observations. First, that in his hospital it was possible to learn how infection arising in the maternity department could lead to infection in the home; and he instanced breast abscess as seen in the surgical wards some six weeks after delivery, and pneumonias occurring in the older members of the family who were admitted to the medical wards. He pointed out that when infection occurred both mother and baby must be isolated. For the last six to eight months in his hospital, colonization of the babies' noses by staphylococci had been prevented by applying Naceptic ointment to the noses of mother and baby. There had been a resultant drop in the incidence of both breast abscess and pneumonia. Secondly, he stated that rooming in was practised with success in his hospital, and that this was possible because of the adequate provision of small nurseries, which allowed the segregation of crying babies without danger of overcrowding. The speaker supported Professor Donald by saying that he also adopted a policy whereby the mothers handled the babies and in which bathing the babies had been abolished. Finally, he suggested that the time might have come when normal maternity patients should only be kept in hospital for forty-eight hours and should then be returned home to the care of a maternity nurse.

PROF. HARE, in reply, stated that he was opposed to the use of antibiotic sprays because of expense and the fact that it was very likely to produce resistant strains of staphylococci. He said that cross infection occurred in nurseries and was due to a nurse who was a carrier of the organism concerned. Such a nurse was covered with staphylococci, in her nose, on her skin and on her clothes, and she could not help transferring the organism to the babies she handled. Nurses who are non-carriers act as transferring agents, being contaminated by infected babies. Therefore, he said, the proper thing to do is to remove the nurse from the nursery and substitute the mother. Referring to those speakers who had advocated a return to the good old days before antibiotic therapy, he pointed out that this was impossible because staphylococci could not be washed off, they could not be eliminated from clothing, and gowns were a useless form of protection. He concluded by stressing the value of chemotherapy and antibiotics.

DR. BARBER replied in general terms and agreed with Professor Donald that bathing was, bacteriologically speaking, a dirty procedure.

HAEMOLYTIC DISEASE OF THE NEWBORN

BY

ALAN MONCRIEFF, *C.B.E.*, M.D., F.R.C.P., F.R.C.O.G.
Nuffield Professor of Child Health
Institute of Child Health, University of London

IN the older literature icterus gravis neonatorum was certainly recognized, as was the fact that when it was familial the first baby usually escaped. In some lecture notes published in 1797 by Dr. Thomas Pole—my children's great, great, great, great grandfather—on which he based his talks to the students of Guy's Hospital, there is a short section on infantile jaundice in which the following are among his headings: "seldom injurious", "children sometimes have the true jaundice", "children affected by the mother", and "the disease more prevalent on the continent". I do not know what the last means but the maternal factor is clearly noted.

Over 25 years ago C. H. Smith in New York pointed out that neonatal jaundice was commoner when the ABO grouping of the child differed from the mother. Although in theory haemolytic disease of the newborn is therefore more often due to incompatibility between the father and mother as regards ABO blood groups than when rhesus incompatibility is present, clinically important disturbance in the baby is more commonly due to the rhesus factor. Why this should be so is not clear and these mild cases seem to me to be worthy of more detailed study to see what are the factors which differ from those present in rhesus incompatibility. Indeed I feel that the time has come for studying why haemolytic disease of the newborn producing severe jaundice does not happen more often, and may not happen at all, even if the stage appears, genetically, set for its occurrence.

It is estimated that 15 per cent of European stock are rhesus negative and American figures suggest that 12 per cent of all marriages are between rhesus negative women and rhesus positive men. Even allowing for the heterozygous father the incidence of 1 in 200 pregnancies for rhesus incompatibility is small. Why is there not more trouble? Women seem to vary in the degree of sensitivity to and their response to the impact of rhesus positive red cells. It has been estimated that only half of rhesus negative recipients of rhesus positive cells develop antibodies. The record seems to be held by a rhesus negative mother who produced twenty rhesus positive foetuses without any production of antibodies. Another curious thing is that when father and mother are incompatible in the ABO system as well as regards the rhesus factor the mother is less likely to be sensitized by rhesus positive cells than when she is compatible with her husband as regards the ABO factor. A study of rhesus negative mothers who do not become sensitized despite the introduction of rhesus positive cells might throw light on preventive measures. (In another field I have long advocated that a study of the reasons for the perfect teeth of the African, for example, might throw more light on dental caries than by studying the patients where this has occurred.)

The infant also varies, as everyone knows, in the severity of the disturbance caused by rhesus incompatibility. About 15 to 20 per cent of rhesus positive infants born of sensitized rhesus negative mothers have no clinical illness although, of course, the Coombs' test is positive. There is sometimes, but not always, a familial pattern as regards the degree of illness in the baby. Occasionally, however, the inexplicable happens. I remember in the early days of work on this subject dealing with a family who after one normal child lost two from haemolytic

disease of the newborn. Pregnant again and with a nasty titre of antibodies the mother delivered herself of a rhesus positive baby who was normal in every way.

What steps can or could be taken to deal with the situation prophylactically? The original suggestion of using "Rh hapten", derived from red cells, which inhibits anti-D serum (Carter) has not been widely accepted as being worth while. Some attempts to use cortisone in pregnant, sensitized women have been disappointing in the results obtained. A more likely line of approach will be mentioned by later speakers but I may be allowed a brief summary here. Diamond had suggested the possibility of using an artificial blood group chimera—i.e., a graft of foetal tissue. Bangham at the National Institute of Medical Research, Mill Hill, has established that in pregnant monkeys it is technically possible to expose the umbilical vein of the foetus at hysterotomy, inject haemopoietic tissue, close the uterus and the pregnancy proceeds normally to term. Professor Lennon and Dr. Tovey at Bristol who are here today are attempting a similar experiment in the human and will tell us about it later. As already mentioned, study of the mother who ought to produce affected babies and does not might indicate the existence of protective factors.

Finally as regards diagnosis there is little to be said. A definite diagnosis depends upon demonstrating the presence of maternal antibodies and the finding of a rhesus positive baby with a positive Coombs' test. Difficulties may arise when dealing with ABO incompatibility with severe symptoms. Occasionally hereditary acholuric jaundice may cause trouble in the immediate newborn period. If antibody testing has not been done then severe jaundice in the newborn may present as a diagnostic problem mainly involving rarities. Congenital syphilis, if severe enough to have produced neonatal jaundice, is usually fatal—a stillborn foetus or early death. Toxoplasmosis, cytomegalic inclusion disease and congenital leukaemia are in the list. Certain rare forms of early infection producing a rapid haemolysis may occur.

There is one diagnostic procedure which carries a risk and I think should be abandoned. This is when an attempt is made to aspirate liquor amnii for bilirubin estimation. Puncture of the placenta could result in the passage of a considerable number of foetal cells into the maternal circulation with a sudden and damaging rise of antibody titre. My colleague, Dr. A. P. Norman, has provided me with an example of this danger.

A woman at twenty weeks of pregnancy had an antibody titre of 64. At thirty-two weeks paracentesis was attempted and the placenta punctured. At thirty-four weeks the antibody titre had risen to 16,000 and a macerated, hydropic, stillbirth occurred at thirty-seven weeks.

Other speakers with more practical experience will be dealing with other aspects of the problem. My contribution is a short survey of certain theoretical considerations which appear to be worthy of more study.

HAEMOLYTIC DISEASE OF THE NEWBORN—*continued:*

FRANK STABLER, M.D., B.S., F.R.C.S.(Eng.), F.R.C.O.G.
Obstetrician
Princess Mary Maternity Hospital, Newcastle-on-Tyne

I INTEND to speak not as a paediatrician concerned in the management of babies affected with haemolytic disease but as an obstetrician looking at the problem as a whole. I have never carried out an exchange transfusion in my life and the inner mysteries of the tests carried out on mothers and babies are a closed book to me. Moreover, I find that a great deal of what I have to say has already been said by Dr. William Walker and Dr. Sheilagh Murray, Lecturer in Child Health and Regional Transfusion Director respectively in my area. Any figures I present are

derived directly from them or from their writings and I pay tribute to them for allowing me to plagiarize in this fashion.

The main contention I wish to put before you is that haemolytic disease of the newborn is a community problem, and the results should be judged as they affect the community and not as the results of one individual or even of one hospital. For one man to claim that his management results in slightly better figures than another is idle boasting, if that man is dealing only with a section of those in the community. Except for minor differences in emphasis, the management of affected mothers and babies is becoming stereotyped and there is little to choose between the survival rates of those paediatricians who are properly skilled in carrying out the techniques demanded.

As Walker and Murray pointed out in 1954, there are four factors necessary for the establishment of good results in a community:

(1) For the most part this is a predictable disease and the nearer we get to 100 per cent prediction the better the results.

(2) For unpredicted cases there should be a simple means of selecting those babies that need treatment.

(3) The proper selection of babies needing treatment.

(4) The efficient performance of the treatment decided upon.

At that time they considered that 95 per cent prediction should be aimed at. They pointed out that the mortality in England and Wales of live-born affected babies was 14 per cent, whereas in Durham and Northumberland it was 7·8 per cent, and they stated as an ideal that the mortality should approach 2 per cent. In 1957 the general mortality for England and Wales was 12·5 per cent whereas in Durham and Northumberland it was 3·5 per cent. I want today to show how near to this (probably unattainable) 95 per cent prediction and 2 per cent mortality we are approaching in Durham and Northumberland.

Prediction

As no satisfactory test has yet been devised for the prediction of ABO haemolytic disease, and as it is not practicable to test all maternal bloods for the rarer forms of immunization such as those due to the sub-groups of Rh, etc., we must leave about 5 per cent as unlikely to be predicted by our present tests. In the years 1956, 1957, 1958 and 1959, we had prediction rates of 86, 87, 85 and 88·5 per cent. It is evident then that the family doctors are playing their part, and I pay tribute to them for achieving such a state of affairs that only once in five or six weeks do we have an unpredicted case amongst 40,000 live births in the two counties. The default is often due to the patient's carelessness or stupidity.

Non-predictable Cases

Ideally 5 per cent was allotted to this category. Most of them would be predictable but the amount of work that would have to be done would be too big to contemplate. If we do not predict them we must have a means whereby they are detected as early as possible after birth. As these babies may be born in places other than special units we must have some simple directions that all practitioners can follow. Our instructions therefore are three:

(1) Routine Coombs' testing of cord blood in the babies of all rhesus negative mothers.

(2) All babies showing jaundice within 24 hours of birth are to be sent to hospital forthwith.

(3) All babies showing deep jaundice within the first week should be referred to hospital.

By this means in the four years we caught a further 6·5, 5·3, 7 and 8 per cent. The totals then of predicted and "picked up" cases in the four years were 92·5, 92·3, 92 per cent, and in 1959, 96·8 per cent. That is, in the last year quoted, only 10 of 315 cases were not recognized because of failure to carry out the tests. In the four years there was a total of 1,139 cases, and of these 139 were stillborn, so we are left with 1,000 in whom treatment was possible.

Proper Selection

This is less my concern than that of my paediatric colleagues who follow me, but I would submit that this is of less importance than the other two considerations—prediction and

efficient treatment. The indications for treatment are widely known and understood. Some may adopt slightly different levels of haemoglobin or cord-blood bilirubin as indications for exchange transfusion but the differences in survival rates will be only fractions of 1 per cent. The law of diminishing returns has come into play because the results of good treatment are so good. It is only with great difficulty that refinements in selection of cases for treatment now show any return in better results. Without arguing that it is the best or could not be improved upon, I give you our schedule of indications for early exchange transfusion:

(1) We do not employ premature induction of labour as part of our management of haemolytic disease of the newborn except in certain cases that I shall mention later.

(2) A cord haemoglobin value of less than 14·8 g. per 100 ml. whatever the bilirubin level.

(3) A cord bilirubin level of more than 4 mg. per 100 ml. whatever the haemoglobin value.

(4) A cord haemoglobin value of 14·8 to 17·7 g. per 100 ml. associated with a bilirubin level of 2·8 mg. or more per 100 ml.

(5) If the husband is homozygous and the woman has already had an intra-uterine death or hydrops from haemolytic disease of the newborn we do induce labour at 35 weeks (or even at 32 weeks if she has lost more than one). In these cases instead of the expected 85 per cent loss we have achieved a 65 per cent loss only.

The Efficient Performance of Treatment

With 700,000 births per annum and an incidence of 5 to 6 per cent, there should be between 3,500 and 4,000 affected babies in each year. Fifteen per cent of these will be stillborn and this leaves about 3,000 liveborn affected babies in England and Wales. When Walker and Mollison (1957) investigated the deaths from haemolytic disease of the newborn in 1953 and 1955 they found that they were distributed amongst 244 hospitals. A few hospitals would have no deaths so that we can safely say that treatment would be spread amongst 250 hospitals. Three thousand liveborn affected babies were dealt with in 250 hospitals, so that the average number of cases in a year in each hospital would be about 12 and only 8 of these would require treatment. We know that many hospitals treat large numbers of affected babies so that it follows that many hospitals treated much less than 8 cases a year. When we come to figures like this we know that efficiency must suffer. However experienced and devoted the attendant may be he cannot possibly produce as good results as where large numbers are being treated. The reason is that the proper management of haemolytic disease of the newborn is not a matter of the skill and knowledge of one man, but of the co-ordination of the activities of a large number of people—paediatricians, obstetricians, laboratory technicians, specially trained nurses and haematologists. The paediatrician must have at his immediate command the services of a transfusion laboratory large enough to be able to produce compatible blood quickly for every known variety of antibody. Time matters a great deal in the management of haemolytic disease of the newborn and we need facilities for rapid, exact estimations of blood states day or night. The attendant must be free to call for repeated tests and supplies without hesitation. These conditions cannot be provided in 250 hospitals throughout England and Wales. The staff in the smaller hospitals may have learnt the technique of management during their training and may wish, from motives of pride, to keep control of their cases when they go out to their own hospitals, but the handicap is too great and needless deaths will occur. If the conditions that obtain in Northumberland and Durham were present throughout England and Wales, there would be 300 fewer deaths per year out of the 400 that do occur. I feel sure that if we took the results of management of haemolytic disease of the newborn in 50 big, well-equipped hospitals in England and Wales the survival rates for treated cases would be almost identical. The differences would be fractions of 1 per cent and all of them would be over 95 per cent survival in spite of slight differences in indications for exchange transfusion and repeat exchange transfusion, differences in obstetric management and in technique but to argue that one method is better than another would be straining at a gnat. It matters little if one team can achieve a 3·2 per cent death rate and another

3·5 per cent when outside these hospitals the death rate is five times as great. What really matters are the results in the whole population.

Now how did we tackle this community problem in the North East Region? In 1949, a conference was called of the obstetricians from the whole area and it was put to them that we should concentrate the management of these cases into a few centres based on the two large maternity hospitals in Newcastle. This was done as part of the National Investigation then in progress. From then on only Sunderland, Middlesbrough and Carlisle accept their own cases but they too are based on the one Transfusion Laboratory. As this one laboratory has the handling of all the blood samples from the area the patients themselves supply all the varieties of testing sera, for the only supply of these is the immunized mothers. *All* the remaining cases come into Newcastle.

In Durham and Northumberland our liveborn, affected mortality rates were:

	1956	1957	1958	1959
Number of cases ..	201	259	248	283
Total Mortality ..	7·1%	3·5%	6·0%	6·0%
Corrected for deaths due to other causes than haemolytic disease ..	3·8%	3·1%	3·9%	3·9%

In applying the correction for deaths due to other causes, we have not subtracted what one might call associated deaths. For example, if labour is induced at term because of haemolytic disease and the baby dies of hyaline membrane disease or pneumonia the death is ascribed to haemolytic disease, for labour would not have been induced if incompatibility had not been present. The deaths include a number of babies with hydrops who survived only a few minutes.

If we take the two Newcastle hospitals out from the Durham and Northumberland totals the mortality rates for liveborn, affected babies are:

	1956	1957	1958	1959
All deaths ..	4·0%	2·2%	7·0%	5·5%
Corrected for deaths due to other causes ..	2·0%	1·5%	3·9%	4·0%

A summary of the four years shows:

1,139 Cases; 1,000 Liveborn; 139 Stillborn (12·2 per cent). Fifty-six babies died, but 20 of these were due to other causes than haemolytic disease of the newborn.

	Prediction	Mortality	
		Total	Due to Haemolytic Disease
Ideal ..	95%	—	2·0%
1956	92·5%	7·1%	3·8%
1957	92·3%	3·5%	3·1%
1958	92·0%	6·0%	3·9%
1959	96·8%	6·0%	3·9%

In a matter so important as this, strategy is counting more than tactics. Tactics can be left to the local commanders, for the casualties will depend far more on the strategy than the tactics. The strategy is obvious—that somehow the hospitals of an area should be persuaded to concentrate all predicted and discovered cases into one or more large central hospitals. Rivalry in accepting cases of haemolytic disease means unnecessary deaths. The casualties will be far fewer if the company commanders will be prepared to draft all those liable to become casualties. Unfortunately my military metaphor does not apply in the medical world. We have to persuade, we cannot order.

If what I have said helps in persuading I am satisfied.

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HAEMOLYTIC DISEASE OF THE NEWBORN—*continued:*

A. P. NORMAN, *M.B.E.*, M.D., F.R.C.P.
Queen Charlotte's Hospital, London

PERINATAL mortality resulting from rhesus incompatibility is in this country still appreciable. Some 4 per cent of stillbirths and deaths in the first week of life are the result of rhesus incompatibility; stillbirths form the larger part of these losses.

Allen and Diamond, probably the leading authorities on the subject, claim that in recent years they have had in Boston a mortality of under 5 per cent in their cases. It should be the aim for all countries dealing with rhesus incompatibility to reach this figure, but it must be admitted that our own mortality at Queen Charlotte's Hospital is still nearer 10 per cent than 5 per cent over the past few years. In any case this figure is exclusive of stillbirths and it would give a more accurate and realistic picture of the mortality if all future published statistics gave the total perinatal mortality, inclusive of stillbirths.

There has been no striking advance in the treatment of this condition in the past decade apart from the use of multiple exchange transfusion in the prevention of kernicterus. An accurate method of assessing the degree of foetal involvement is still required, and even more valuable would be a way of preventing maternal iso-immunization. In default of these, the foetal and neonatal loss can be reduced significantly only by careful assessment of all the evidence and by efficient teamwork of pathologist, obstetrician and sometimes paediatrician.

A lowering of the mortality is likely to be obtained in centres where a reasonable degree of efficiency already has been obtained, only by reducing the numbers of those infants born too severely affected to be saved, or who are stillborn. In the latter group prematurity is the limiting factor, but the outlook after 32-weeks gestation is, in my opinion, considerably better for the child slightly affected than the same child two to three weeks more mature but severely affected.

There need be no anxiety that the weight of the rhesus-affected infant at 33 weeks onward will be excessively low.

Examples were given of management in recent instances of bad previous history and of sharply rising maternal antibody titre.

DISCUSSION ON HAEMOLYTIC DISEASE OF THE NEWBORN

DR. TOVEY drew attention to the fact that there was a high risk in certain first affected babies. He showed the following table to show the relationship between the antibody titre and the foetal risk in such cases.

Titre	1:10	1:10–1:20	1:20
Stillbirths	0	1%	21%
Stillbirths or neonatal deaths	0	2%	30%

He said that 2 out of 3 stillbirths in these cases occur after the 37th week and therefore he recommended induction of labour three weeks before term where the antibody titre was more than 1:20.

For cases of rhesus incompatibility occurring after the first affected baby he gave the following figures:

Titre	1:10	1:10–1:20	1:20
Stillbirths	0	8	25
Stillbirths or neonatal deaths	0	13	40

With the first affected child he said the total loss was 10 per cent and 23 per cent with subsequent affected cases. In the latter group 43 per cent of stillbirths occur before the 32nd week.

He went on to describe the suggestion by Diamond that fresh rhesus-negative haemopoietic tissue might be injected into the affected foetus

in utero at about 14 to 20 weeks of pregnancy with the idea of producing a blood chimera. He thought that if this were to be attempted cases should be carefully selected and suggested that a woman with rhesus-negative blood married to a man with homozygous rhesus-positive blood and who had already given birth to two stillborn babies might be a suitable subject for such treatment.

PROF. LENNON (Bristol) then described his attempt to carry out this treatment in just such a case. He described his difficulties both in experimental work on sheep and on the patient. The case was first seen at the eighteenth week of pregnancy when the antibody titre was over 1:20. He had made a lower segment incision in the uterus and the patient was placed in a steep Trendelenburg position to try and conserve the liquor; this, however, rendered the cord difficult to find as it fell away to the fundus. The loss of liquor caused uterine contraction and the attempt failed. The foetal haemoglobin concentration was found to be only 50 per cent. He said that he felt the operation was feasible and wondered whether injection into the peritoneal cavity of the foetus might not be easier.

DR. SOPHIAN (London) next spoke and asked where the haemolysis of the foetal blood occurred; he suggested that it could occur in the kidney, and then suggested that by injecting radioactive isotopes into the maternal blood it might be possible to protect the foetal kidney and prevent the haemolysis.

DR. D. A. BEVIS (Manchester) said that he considered amniotomy a safe and useful procedure, and that in his area it was not possible to obtain antibody titre estimations and that they relied upon the evidence obtained from examination of the liquor. He himself had done 250 cases of amniotomy, and Walker had done 100. In only 1 per cent of cases was there a bloody tap. He did not think that the objection that the procedure might result in direct injection of foetal cells into the maternal blood was important. It was well known that the development of haemolysis could occur very rapidly, and the cases described by the opening speakers need not necessarily have been due to the amniotomy.

DR. COPE (Birmingham) thought that Mr. Stabler had divorced diagnosis from treatment. He considered that treatment could be standardized but that diagnosis was all important. There was a danger in concentrating all cases of rhesus incompatibility in selected centres in that students and housemen might not be properly instructed. He suggested that Flying Squads might be organized to perform the necessary treatment.

PROF. MCCLURE BROWNE (London) strongly supported the safety and value of amniotomy which he had carried out on more that 250 occasions with no trouble. He thought that routine induction of labour at the 38th week of pregnancy was the right treatment in most cases, as there was little to gain in the two remaining weeks of pregnancy as regards size and maturity but that there might be much to gain as regards the incompatibility. If induction had to be performed at the 32nd week, then he thought Caesarean section should be done if the patient was not in labour within 24 hours. He went on to say that he had made two attempts at injection of foetal haemopoietic tissue; the first case at the 20th week of pregnancy had been lost 6 weeks later, but the second case was now in the 33rd week and there had been no rise in the antibody titre.

MR. STALLWORTHY (Oxford) described a case of erythroblastosis occurring in the child of a rhesus-positive woman, and gave a warning that high antibody titres were still being produced by mismatched blood transfusion. The first baby may sometimes be affected even in the absence of a previous history of transfusion, and he suggested that some of these cases may have been given autogenous blood as children for some condition such as malaena. Therefore he said it was important to check all firstborn children in rhesus-negative women. He asked Mr. Stabler if the cases described in his series represented affected babies or babies from

mothers in whom antibodies had been found. Finally, he made a plea for the use of perinatal figures in statistics and the abolition of corrected figures.

All the opening speakers replied. MR. STABLER poured scorn on the idea of a Flying Squad for the treatment of babies with rhesus incompatibility, asking how it could carry all the necessary sera and blood for transfusion. He was not strongly opposed to induction at thirty-eight weeks but said that it was not an entirely innocuous procedure. In answer to Mr. Stallworthy he said that his cases represented affected babies. DR. NORMAN pointed out that exchange transfusion was a skilled procedure and must not be carried out by inexperienced people.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

OPENING OF THE NEW BUILDING

By 2 p.m. on 13th July, the forecourt of the new College was a scene of bustling activity, with Fellows and Members and their wives and friends hurrying in to take their seats in the Nuffield Hall. The varied hues of the ladies' dresses gave colour to the scene, and on this occasion the male half of the assembly vied with them; the demand for Fellows' and Members' gowns was so great that it exceeded supply, and the gowns and hoods of many universities were also on view. The weather was that of a typical 1960 summer day, "cloudy with scattered showers", but it did not spoil the great occasion.

While Her Majesty's arrival was being awaited in the Nuffield Hall, three processions passed in turn to their seats; first, the Presidents of the other Royal Colleges and Faculties and other distinguished guests; then the past Presidents of the College with the past Chairman of the South African Regional Council; and last, the Council of the College.

Her Majesty was met on arrival by the Minister of Health and by the Mayor and Mayoress of St. Marylebone. After being presented to Her Majesty in the entrance hall the President, Sir Andrew Claye, presented Lady Claye, the other officers of the College, the Chairmen of Regional Councils or their representatives, the Bishop of London, and the Secretary of the College. They then followed Her Majesty in procession to the Dais in the Hall. On arrival, Her Majesty was presented with a bouquet of flowers by Miss Annabel Jackson, daughter of the Honorary Secretary.

President's Address

May it please Your Majesty—

It is my privilege to express on behalf of all the Fellows and Members our tremendous delight and joy that you are honouring us by opening our new College building.

This to many of us is a day of memories. Among these I particularly have in mind 5th December, 1932, when Your Majesty's Father and Mother, then Duke and Duchess of York, opened the Florence Blair-Bell house, 58 Queen Anne Street, given to us by our first President, William Blair-Bell, when the College, from being a small body of men and women, became also the geographical home of British gynaecology.

Some of your audience today, Ma'am, were present then, when Blair-Bell and his Honorary Secretary, William Fletcher Shaw, supported by the leading gynaecologists of the British Isles and of the Commonwealth, passed that important milestone on the way towards the realization of their ideals.

We have left our old home not without a certain proper nostalgia, and the vital place in our history occupied by these two men is recognized by the plaque put up to them in the Entrance Hall here.

The next ceremony which I wish to recall is Your Majesty's own admission to the Honorary Fellowship on 17th July, 1951, a red letter day for us, when you were sponsored by Sir William Gilliatt and Professor R. W. Johnstone.

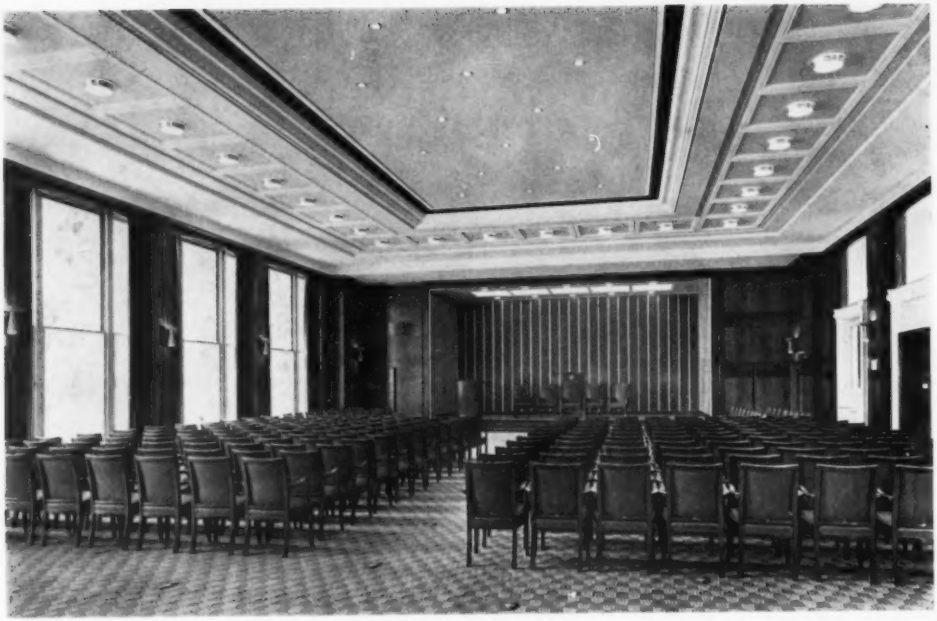
In 1957, after Lord Nuffield's munificence had encouraged us to proceed to obtain a site and plans, came the third occasion, still fresh in the minds of Fellows and Members—the laying of the Foundation Stone here on the afternoon of 6th November, by Her Majesty Queen Elizabeth the Queen Mother.

We are grateful to Messrs. Louis de Soissons, Peacock, Robertson and Hodge, our architects, and to Messrs. Gerrards our builders, and their staff—those who planned, and those who brought the plans to fruition in this beautiful building.

Returning to today, we are specially happy, Ma'am, that your opening of this College falls

[*Photograph by Central Press Photos, Ltd.*

OPENING CEREMONY



THE NUFFIELD HALL

in the year of the birth of Prince Andrew, whose progress we are following with the lively attention common to all your loyal subjects, heightened by the special interest we feel in our most distinguished Fellow's new baby.

Let us then continue our forward march, warmed and heartened by Your Majesty's presence here today, by the presence of many colleagues and friends, and better placed physically than ever before. May this College building be the outward and visible sign of an inward and spiritual urge that will continue to generate advances in obstetrics and gynaecology throughout the British Commonwealth.

May I now ask Your Majesty formally to declare the College open, and to address us?

Her Majesty the Queen's Speech

Mr. President,

Thank you for your warm words of welcome.

I am delighted to be here today for many reasons. My family, as you have pointed out, has had close associations with the Royal College of Obstetricians and Gynaecologists since its foundation. Nine years ago, almost to the day, I myself was admitted to an honorary degree of this College. Such a degree is more usually given to those who practise an art or science than to its beneficiaries, but I have always been proud of my Honorary Fellowship, and it is a happy chance for me that the opening of your new building gives me the opportunity of expressing in the presence of Fellows and Members of this College my personal thanks to those of your great fraternity to whom I owe so much.

For more than thirty years the College has grown in influence at home and prestige overseas. During this period medical science has seen vast, indeed revolutionary, advances. The application of these advances in its own special branches of medical practice has been one of the great achievements of the College, with the result that expectant mothers can look forward calmly and confidently to the birth of their babies.

Indeed you have given almost literal meaning to Wordsworth's assertion that "our birth is but a sleep and a forgetting", and have done much to ensure, if I may take my second son as an example, that "Heaven lies about us in our infancy".

All medical experience must be handed on and I particularly commend the work of the College as an enthusiastic and stimulating guide in the field of education. Its wise counsel has always been at the disposal of those concerned with the general health of the people of this country and indeed of the Commonwealth, whose representatives I am so glad to see among you. These new premises provide a magnificent home for fostering the present purposes of the College and its future responsibilities.

I now declare this College building open and I wish prosperity to all who study and work within its walls.

The Bishop of London then said a prayer.

Honorary Treasurer's Address

Your Majesty, it is a great privilege for me to thank you on behalf of Council, for so generously consenting to open officially our new home, and for the gracious way in which you have done so today.

It is not only Council but every single Fellow and Member of this College who would wish to express gratitude to you Ma'am. This is for us a day of historic significance, being the culmination of a project initiated by our beloved Patron, Your Majesty's Mother, when she laid the foundation stone nearly three years ago. In progressing from our small College House in Queen Anne Street to this magnificent building of which we are all so justly proud, we feel that we have a real College wherein future generations of medical men and women, devoted to our discipline, will find inspiration and opportunity to advance knowledge.

Thanks to the generosity of Sir Stanford Cade, a painting of this Opening Ceremony is to be completed by Mr. Terence Cuneo and hung on the main staircase, as a reminder to all those who succeed us in the years to come of this memorable day on which Your Majesty has honoured us with your presence.

Council felt, Ma'am, that it would like to offer to you a very small token of appreciation. As

today's ceremony has followed so soon upon the birth of Prince Andrew, we thought that it might be not inappropriate that this token gift should be *The Oxford Dictionary of Nursery Rhymes*. We have had a copy bound and embossed with the College crest. We ask with humble duty and gratitude that you accept this as what I might call a "Sunday copy". We thought, however, that Prince Andrew himself would prefer a less ornate edition for his future delectation in the nursery, or even maybe to gratify those destructive instincts inherent, I suspect, even in small Princes.

And so Ma'am, may I offer you these tokens of our gratitude and once again thank you for being here today.

. . . . . .

Her Majesty then left the Hall, followed by the Dais party, and made a tour of the building escorted by the President. Representatives of the architects, the builders, and the workmen were presented in the entrance hall before Her Majesty entered the Library. There the Honorary Librarian, the Consultant Librarian, and the Honorary Curator of the Museum were presented, and Her Majesty showed interest in the Chamberlen instruments, newly mounted in a display cabinet, and the photographs relating to them which were shown alongside.

Her Majesty proceeded to the Museum, where the Consultant Pathologist and the Assistant Curator were presented. The Museum was occupied by those guests of Fellows and Members whom it had not been possible to accommodate in the Nuffield Hall. By courtesy of Messrs. Smith, Kline and French these guests had been able to see the ceremony in the Hall on closed circuit colour television, accompanied by a spirited commentary from Mr. John Stallworthy.

Her Majesty was then escorted up to the Committee Room, where members of Council, past Presidents, the past Chairman of the South African Regional Council and the Honorary Fellows were presented. After passing through the Council chamber, where the Presidents of the other Royal Colleges and Faculties, the Vice-Chancellor and Principal of the University of London, benefactors of the College, and other distinguished guests were assembled, and after signing the Visitors' Book and a photograph, Her Majesty went on to the President's Room for tea with members of the Dais party and the wives of the Officers of the College, of the Chairman of the Australian Regional Council and of the representative of New Zealand, who were then presented. When Her Majesty left the President's Room, a very enthusiastic gathering outside the Nuffield Hall and below in the entrance hall expressed by their applause their gratitude for the gracious visit. Just before leaving Her Majesty unveiled the tablet commemorating the ceremony. It was an unforgettable day in the history of the College.

The evening of 13th July was left open for private hospitality.

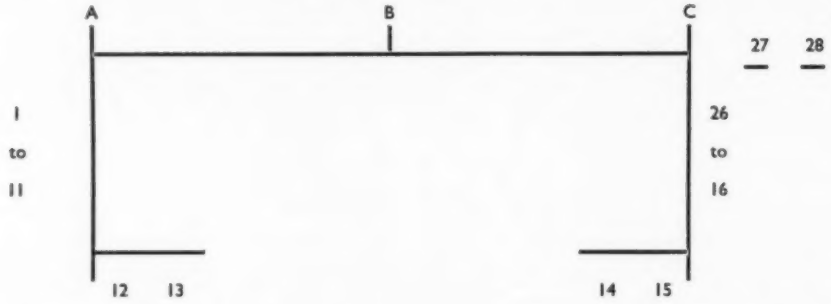
On the evening of 14th July, by the kindness of the University of London, a reception was held in the Senate House, graced by the presence of the Patron of the College, Her Majesty Queen Elizabeth the Queen Mother. During the course of the evening members of Council and their wives, and many other Fellows and Members of the College and distinguished guests were presented to Her Majesty.

On the evening of 15th July, by courtesy of the Lord Mayor and Corporation of the City of London, the Annual Banquet was held in the Guildhall, about 600 members and guests being present. After a short speech by the Lord Mayor, Professor John Bruce, President of the Royal College of Surgeons of Edinburgh, proposed the toast of the College, and the President replied. The toast of the guests was proposed by Mr. Donald Fraser, F.R.C.O.G., and the response was made by Mr. T. G. Wilson, President of the Royal College of Surgeons in Ireland. The opportunity of dining in these historic surroundings to wind up the proceedings of a momentous week was very much appreciated by Fellows and Members.

[*Photograph by courtesy of the "Nursing Mirror"*

THE LIBRARY

THE COUNCIL—JULY, 1960



A. The Honorary Treasurer
(Sir John Peel)

1. The Vice-President, Mr. S. W. Maslen-Jones
2. Prof. J. C. McClure Browne
3. Dr. T. F. Corkill (New Zealand)
4. Dr. D. F. Standing (South Africa)
5. Mr. Naunton Morgan (Representative of the Royal College of Surgeons)
6. Mr. Humphrey Arthure
7. Mr. F. Stabler
8. Mr. Hector MacLennan

B. The President
(Sir Andrew Claye)

9. Mr. L. B. Patrick
10. Mr. Gavin Boyd
11. Mr. Stanley Clayton
12. Mr. S. D. Loxton
13. Dr. M. I. Cookson (D.Obst.)
14. Dr. J. G. Gallagher
15. Miss Gladys Hill
16. Dr. M. Garrey
17. Dr. Wallace Barr
18. Mr. H. J. Malkin
19. Mr. W. Hawksworth

C. The Honorary Secretary
(Mr. Ian Jackson)

20. Dr. A. G. Cumming (New Zealand)
21. Mr. Arthur C. H. Bell
22. Prof. T. N. A. Jeffcoate
23. Mr. J. Tomkinson
24. Dr. Ninian Falkiner
25. Dr. R. B. Charlton (Australia)
26. The Vice-President, Mr. G. F. Gibberd
27. The Secretary, Miss W. E. Mallon
28. Clerk, Miss J. Brightman

MEETING OF COUNCIL

AT the meeting of Council held in the College on Saturday, 24th September, 1960, with the President, Sir Andrew Claye, in the Chair, the following were admitted to the **Membership:**

Augustus Amartei Armar.
Christian Bam.
Dhirendra Nath Banerjee.
Sreemanta Kumar Banerjee.
Norman MacGregor Downie Blyth.
Pauline Mayda Bousquet.
Alan Harold Bradfield.
Geoffrey Frank Bradfield.
Ian Terence Brake.
Tancred Busuttil.
Ian Egerton Cary.
Kenneth Leslie Collins.
Joan Marie Curtis.
Lawrence Stanley Deane.
Marie Therese D'Netto.
Robert Franklin Heys.
Ma Hla-Kyi.
Florence Ponnuthai Isaiah.
Walter Ian Harewood Johnston.
John Booth Jones.
Karapati Kanakadurgamba.
William Kelso.
John Francis Kemp.
John Frederick Leeton.
Joseph Luxmoore Marcus.
Jimmy Maneckshaw Mistry.
William Michael Moore.
Edwin David Morris.
Barun Kumar Mukherji.
Olusola Adewole Ojo.
Peter Robert Bradley Pedlow.
Wilfred Samuel Emmanuel Perera.
Walter Pollard.
Doreen Rothman.
Anjul Kumar Sinha.
Sarel Johannes Smal.
Alan Malcolm Smith.
Herbert John Solomon.
Bruce Sutherland.
Thomas Edgar Torbet.
Alan Robert Trist.
William Leslie Whitehouse.

Presentation of the Eardley Holland Gold Medal to Professor Chassar Moir on 14th July, 1960

Sir Henry Dale's Speech

Mr. President, Ladies and Gentlemen: I am indeed grateful for the opportunity of being present at this meeting, and of adding a brief, personal tribute, to the general acclaim with which this assembly has just greeted the first award of the Eardley Holland Medal of this Royal College, to Professor Chassar Moir, and its presentation to him by the donor in person. It was my privilege to be brought into contact with Professor Moir more than a quarter of a century ago. He was then becoming known as an able and enterprising Obstetrical Registrar; and he was just about to enter upon the important clinical researches, in special recognition of which your award of this Medal has so fittingly been made.

When Dr. Moir first came to see me, he had been asked by the Medical Research Council to undertake a clinical comparison of the activities, in practical Obstetrics, of two long-known alkaloids from ergot. Experimental studies in the laboratory, my own among them, had failed to detect any difference between the actions of these two substances; but claims were then being made for one of them, to be the only one of value in practical obstetrics; and such a claim could be put to the test only by a comparative clinical trial. I encouraged Dr. Moir to undertake this; and I specially welcomed his decision to use a method which would enable him to obtain objective, mechanical records of the tone and rhythmic activity of the puerperal human uterus. Using this, he was very soon able to answer the question which had been put to him. These two alkaloids were as indistinguishable in their actions on the human uterus, thus recorded, as they had been in the more general comparisons made by laboratory experiments. And Dr. Moir's clinical experiments showed a further point of identity between them, namely, that neither of these known ergot alkaloids had any significant action on the human uterus when it was given by the mouth; both of them had to be given by injection to have any such effect.

This last observation presented Dr. Moir with the opportunity of tackling a different problem, and, as it proved, of making a much more important discovery. The old, watery "Liquid Extract of Ergot", which had figured so long in the British Pharmacopoeia, contained neither of these known alkaloids; and, even if they had been present, they could hardly have given this watery extract an action useful in Obstetrics, since it was always administered by the mouth. Yet many experienced clinicians, obstetrical specialists as well as general practitioners, had clung to its use and seemed still to be confident of its value. Was it possible that, after all, it might contain some other active principle, which all our laboratory pharmacology had entirely failed to detect? Dr. Moir had obviously developed, and now had ready to hand, the ideal method for putting such a possibility to the test of an objective clinical trial. And again the result came quickly and decisively. The old, then widely discredited, but by others still loyally advocated Liquid Extract of Ergot, was shown to contain something different from the known alkaloids, something which was readily absorbed from the stomach, to produce the desired stimulating effect on the human uterus.

Nearly three years were then needed, however, before my chemical colleague, the late Harold Dudley, in intimate collaboration with Chassar Moir at every stage, was able to isolate the principle responsible for this activity, and to identify it as a previously unknown and simpler alkaloid, Ergometrine—now everywhere recognized as *the* constituent of ergot required in obstetrics—the unknown active principle, which we laboratory pharmacologists had been seeking

THE EARDLEY HOLLAND GOLD MEDAL

for so many years, but seeking in vain. And the use of ergot in obstetrics thus acquired not only a new convenience, but a precision and safety which it had lacked.

These researches not only marked Dr. Chassar Moir as a coming leader in his own speciality; they provided also, it seems to me, an early and a brilliant example, of the now so common, but then so unfamiliar, use of the objective methods and criteria of experimental science, in the conduct of researches of many kinds in the clinic. And I am sure, then, Mr. President, that your Royal College is worthily celebrating not only a great, but a widely influential achievement, in this first award of the Eardley Holland Medal.

In reply PROFESSOR CHASSAR MOIR said:

Mr. President and members of Council, Sir Eardley Holland, Sir Henry Dale, Fellows and Members, I am deeply moved by your kindness.

Sir Eardley Holland, you are a great midwife. You were one of those present at the birth of this College. And it was you who guided the College during its years of consolidation—a time well known to all parents as the difficult late teen-age period. I was proud to work under you then. You have now rounded off your work by giving this splendid award which will be for ever a stimulus to obstetricians in Britain, and throughout the great British Commonwealth.

Sir Henry Dale, you it was who paved the way for the research that led to the discovery of ergometrine, and you were the Father to whom we repeatedly turned for guidance. Your name will always be linked with ergot and the remarkable results of your many discoveries in this field.

I must also speak of my old and lovable chief, Francis J. Browne, who initiated the research on the clinical effects of ergot and staunchly supported the work to its successful conclusion.

My collaborator and friend, Harold W. Dudley, is alas no longer with us. It was his dogged perseverance and uncanny insight into chemical mysteries that finally caused the ergot fungus to yield up its richest prize. And it was an irony of fate that his final paper describing the exact chemistry of ergometrine and its method of preparation—free for everyone to copy, without thought of patent rights or financial gain—should have been published on the very day that he himself succumbed to a fast advancing, fatal illness. Let us remember him in honour now.

Gentlemen, it would be false modesty to disguise the fact that I am indeed proud that this, the first Eardley Holland Medal, should come to me, but I am still prouder that, 25 years after its discovery, British Ergometrine should have a Jubilee Celebration of its own, and that this should be linked with the name of Eardley Holland.

DISCUSSION ON THE FUTURE ACTIVITIES OF THE COLLEGE

THIS discussion took place on 14th July in connexion with the opening celebrations of the new College Buildings. Mr. J. M. Chesterman of Sydney, Australia, was in the Chair.

PROFESSOR JAMES LOUW (Cape Town) was the first opening speaker. He said that although the fine traditions of Queen Anne Street would certainly be carried to Regent's Park there was no room for complacency. In the words of Samuel Johnson: "The future is purchased with the present." Have we still the restlessness of explorers, with the courage to bring imagined ideals to fruition? Are we so enthralled by active work that we stimulate those around us by our example?

In obstetrics we must see that normal pregnancy and labour (including their psychological aspects) are adequately studied. In the past major advances in medicine, including the control of sepsis and the use of anaesthesia, have come from obstetricians; a future obstetrician may solve the mystery of hypertension or of epileptiform fits. In gynaecology there are also great opportunities. Understanding of the control of menstrual cycles would make much of the surgery of today unnecessary. Genital cancer, which is relatively accessible, lends itself to research and to study of its endocrine background.

Professor Louw suggested that the title of the College is unwieldy. As he considered the term "gynaecology" included midwifery, the designation "Royal College of Gynaecologists" should be sufficient.

He also deplored the fact that a higher surgical qualification is still necessary to obtain certain appointments. The Membership examination should be of a sufficient standard to justify appointment to any post in our branch of medicine. The examination might also be conducted in Commonwealth countries, as the cost of travel is so high that a young man prefers to secure any higher qualification that is available in his own country. In South Africa a new College of Medicine, Surgery and Gynaecology has been formed, and in the formation of any new college we should use our influence to ensure the recognition of gynaecology as a basic discipline. So many new colleges and institutes are being formed that there might be a place for a co-ordinating body.

In world politics medical men have not played their full part. Medical science has been chiefly responsible for the recent growth of population, but we have shunned the study of genetics and family limitation. We cannot go on living and multiplying haphazardly. The great aim of improving the mind, health and happiness of mankind can be partially attained by the assurance of physically and mentally happy womankind.

MR. HECTOR MACLENNAN (Glasgow) was the second speaker. He said that although the College was only just over thirty years old in that time it had established standards of education and hospital training. The College has always insisted on the need for thorough training as well as examination for candidates for the Membership and Diploma. Research has been promoted by travelling scholarships, and knowledge has been publicized by lectures and in our own Journal. We act as advisers to the Ministry of Health and to many government departments, and many Fellows and Members serve on administrative committees of the

National Health Service, on Royal Commissions, and on governmental enquiries. In the future we must promote and foster all these past activities, but we must not rest complacently on our record. Removal to new premises was essential to allow further expansion of our activities.

Perhaps the most significant feature of our College is its Commonwealth association; at present we are the only Commonwealth medical college, and we have established Dominion Regional Councils. We should form a Commonwealth Relations Committee to study and foster this association, including that with countries in which there is no regional council. In the words of the Prime Minister: "The Commonwealth relationship is not something which can be left to look after itself. It needs a positive and continued effort in understanding . . . not only at the level of political leaders . . . It must extend into all walks of life."

Honorary Lectureships could be increased with advantage at home, and also in the capital cities of the Commonwealth, and research might be stimulated by prizes and scholarships. The College might itself initiate research into particular problems through scientific committees. Reports that have emanated from the College on Maternal Health Services and on Maternity Hospital Construction have been of great value, and we might now well consider and report on the ideal staffing structure for professorial units, other teaching units, non-teaching units and peripheral hospitals.

While it is appreciated that some Commonwealth countries have their own obstetrical qualifications, which we respect, we should make it our aim that our overseas colleagues will wish to take a British higher qualification, and posts must be established so that they can study here rather than drift to the continent or exclusively to the United States of America. Furthermore, we must encourage a two-way traffic, so that our young men may travel abroad during the formative period of their training.

We should encourage our Fellows and Members, both from home and abroad, to make full use of this splendid building. The Library is notable for its rare books, the Museum contains rare specimens, and the Laboratories are available. When finance allows it we should provide a centre where we can offer hospitality to our visitors and share comradeship with our colleagues.

It is written in the Book of Proverbs: "Where there is no vision the people perish." By its vision, therefore, let the College flourish.

MR. ARTHUR BELL (London) was the third opening speaker. He referred to the difficulties that had been overcome in the past, at the time of the foundation of the College, and in carrying out the plan to rebuild. Our fine new building must not merely contain a dull and silent collection of specimen bottles, books and so forth, essential though these are for College activities. The common rooms should be used as a place where colleagues from overseas or the provinces may meet, and in this hall dinners for travelling clubs or others connected with obstetrics and gynaecology may be held. The hall also provides ample accommodation for our endowed lectures. Consideration should be given to the needs of the large body of diplomates—special lectures for their benefit would be appreciated, although these should not take the form of courses as preparation for examinations.

The laboratories will at first be used for the service of the museum and the Rare Tumour Registry, but it is to be hoped that research teams will soon be working here. The three prerequisites for research are finance, worthwhile projects and research workers—given finance the others should raise no difficulty. We should strive to obtain new money for research, either as outright gifts or to sponsor particular projects.

As a Commonwealth College we have always taken a special interest in the training of postgraduates and in the interchange of knowledge with colleagues overseas, and to this end the Sims Black Travelling Professors have contributed much. At present our charter and regulations only allow graduates from universities whose degrees are recognized by the General Medical Council to sit for our examinations, and the rigidity of this rule is harmful to some regions in Asia and Africa where our help is most needed, and whose doctors find it impossible to satisfy our standards of training. The

problem is an urgent one, not only for the post-graduates concerned, but for the College itself. If we do not move in this matter many of these peoples will institute their own degrees in obstetrics and gynaecology.

The interchange of trainees, particularly at registrar level, between teaching and non-teaching units has been very successful in this country, and the College has been able to place a few nominees of Dominion Regional Councils in house appointments over here. Could not the College initiate and foster a wider interchange of trainees between teaching units in this country and those in the less developed areas of Africa and Asia? The wealth of clinical material overseas and the experience gained here would be of great benefit to both parties.

We are proud of the *Journal of Obstetrics and Gynaecology* which is issued under the direction of our College. We owe a debt of gratitude to Professor James Young who has been its editor for many years. Its circulation increases annually and its high standard is appreciated throughout the world. We intend to maintain its standard and increase its circulation.

Thirty years ago our founders foresaw many difficulties, but regarded them as things to be overcome; that is why they incorporated the words "Super ardua" in our coat of arms. May these words be our guiding light in years to come.

DR. J. SOPHIAN (London) urged the College to initiate research particularly into renal function about which he thought there was a distressing lack of inquisitiveness. He went on to discuss the relationship between the kidney and toxaemia and illustrated his remarks by several slides of the kidney.

DR. R. A. KINCH (London, Ontario) said that in his view there was no fear of the flow of graduates who wished to come to the United Kingdom diminishing. He thought however that the main difficulties were financial and he suggested the exchange of posts, salaries, residences, and even perhaps children. One of the functions of the Regional Councils should be to produce the means whereby graduates could come to Britain.

MR. ALAN BREWS (London) said that he was speaking by virtue of his position as Honorary Curator of the Museum. The museum at present has five to six hundred specimens but can hold five to six thousand. His desire was to see not only greater quantity, but more important, greater quality. He hoped that donors would not mind their specimens being returned, destroyed or allotted to the examination collection. Specimens were wanted from all parts of the world; they could be either individual specimens or collections, preferably already mounted. He particularly asked for specimens which would illustrate disorders peculiar to the donating region. In conclusion he asked for not only wet specimens but also for colour transparencies, slides, photographs and X-rays.

DR. LLEWELLYN-JONES (Kuala Lumpur, Malaya) stressed the importance of the Commonwealth link and spoke for members, like himself, who came from areas not represented by a Regional Council. In Malaya he said there were four gynaecologists to serve a population of six million people. It was difficult to get Malayan graduates accepted for posts in Britain despite their good quality. There were large fields of research untapped and he asked could not the College improve and extend the interchange system so that it applied between all Commonwealth countries.

MR. GREEN ARMYTAGE (London) reminded the audience how the Royal College of Physicians and the Royal College of Surgeons had successfully appealed to have their charters altered so that they could allow any graduate from any part of the world to sit for their higher qualifications. This was not the case with the M.R.C.O.G. and he made a strong plea that efforts should be made to alter rule 10 of the Charter. He said that we must encourage Commonwealth graduates to come and sit for the M.R.C.O.G. or they would by-pass the college and take other diplomas.

PROF. IAN DONALD (Glasgow) stressed the need for more science in obstetrics and gynae-

cology. He would like to see the rules for election to the F.R.C.O.G. revised so that a member could be admitted for work of worthwhile scientific value, irrespective of his age or seniority. He did not think that finance was a limiting factor in research, men and ideas would be forthcoming if encouraged. He would like to see meetings held in the College House at which research workers could discuss their current work and exchange ideas, and the proceedings of such meetings should be published.

Miss M. K. Lawlor (Brighton) endorsed the plea made by other speakers for graduates from other countries, mentioning particularly those from India and stating that women more often than men were disappointed by their inability to obtain recognized posts in this country.

Mr. A. P. Bentall (Norwich) was pleased to hear that the more senior members of the College had not forgotten those members in the provinces of this country who had a desire to keep in touch with their colleagues.

Mr. W. G. MacGregor (London) endorsed what other speakers had said about graduates from the Commonwealth and made a plea for a less rigid attitude towards the examination regulations and requirements.

The Chairman in closing the discussion mentioned that he, personally, had a preference for maintaining the Commonwealth link but felt bound to point out the growing Australian tendency towards autonomy. He cited the example of the Royal College of Australian Physicians and Surgeons and the views of the Postgraduate Medical Federation of Australia that it was unnecessary for graduates to travel in order to gain experience or qualifications. The two main problems were the requirements for the M.R.C.O.G. and the fact that the examination had to be taken in Britain.

Acknowledgment

The Editors are indebted to Mr. A. J. Wrigley and Mr. R. M. Feroze for their help in reporting the Proceedings of the Scientific Meeting.

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CERVICAL PREGNANCY

BY

T. S. PISARSKI

From the I Clinic of Obstetrics and Gynaecology Medical Academy, Poznań, Poland

MANY authors state that cervical pregnancy is an extremely rare condition. There are some, however, who believe that it is more frequent than the reports suggest and that it escapes notice by ending in a very early abortion.

The Viennese pathologist Rokitańsky, in 1860, is credited with being the first to introduce the term "cervical pregnancy". The description of his case does not, however, fully correspond to the modern conception of cervical pregnancy.

Much earlier, as far back as 1817, E. Home presented a sectional specimen of female reproductive organs. His report seems to have been the first clear demonstration of the condition (Schneider and Dreizin, 1957).

Schneider's report in 1946 is regarded as the first case of cervical pregnancy with a thorough clinical and pathological documentation. It is very difficult to establish the exact number of cervical pregnancies out of all the cases published up to date. Many authors failed to present evidence necessary for making an undisputable diagnosis. A review of world literature by Dubuis (1950) brings the total to 60 cases. This number must however be taken with great reserve.

Studdiford, in 1945, after a review of the world literature on the subject, found a full documentation only in 14 cases. He added to them 14 other instances diagnosed on clinical findings.

In 1957 Schneider and Dreizin, in a survey of the original papers of all obstetrical records on cervical pregnancy, accepted only 17 cases proved by morphological examination of post-operative specimens or material obtained at autopsy. It must be stressed that none of the cervical pregnancies published so far terminated in a delivery of a viable baby. Our case of cervical pregnancy was studied in the I Clinic of Obstetrics and Gynaecology, Medical Academy, Poznań. The patient was delivered of a living infant at 35-weeks gestation.

CASE REPORT

The 36-years-old patient, S.T., B.C.Nr. 6981/57, was admitted on 3rd October, 1957, at 14-weeks gestation with a previous diagnosis of a tumour in the right adnexa.

Past Medical History: At one time the patient had inflammation of the maxillary sinuses and had complained of frequent tonsillitis, laryngitis and "colds". Since 1956 the patient had been treated for pulmonary tuberculosis.

Obstetric History: The menses started at the age of ten. Thereafter the menstrual periods occurred every twenty-eight to thirty days and were of 2 to 3 days' duration, painless, with scanty flow. During 1945–1952 her menstrual periods were irregular with profuse flow and lasted longer. She had received hormonal therapy but without any improvement. The disorder ceased after curetting. In August 1956 an 8-weeks gestation was terminated on medical advice on a diagnosis of active pulmonary cavernous tuberculosis. Six weeks later, at a gynaecological follow-up examination, the patient was found to have a tumour of the size of a walnut in the pouch of Douglas, arising apparently in the right adnexa. She had her last menstrual period on 13th June, 1957. Examination in September 1957 revealed a 12-weeks gestation and a tumour the size of the fist located in the pouch of Douglas.

The general condition of the patient was good on admission. The pulse, the temperature and the laboratory tests were normal. A gynaecological examination showed the vagina to be 2-fingers wide, and both the posterior vault and a part of the posterior vaginal wall presented a marked convexity due to the tumour descending into the pouch of Douglas. The vaginal portio was soft, distended, short, cylindrical, situated

at a level just below the pubic symphysis. On abdominal palpation a cystic-type growth, the size of a foetal head, slightly mobile, was felt in the front of the small pelvis. Just behind it, in the Douglas pouch, another tumour-like structure, the size of a 14-weeks pregnancy, was also palpable. In view of the tumour in the right adnexa complicating pregnancy, a laparotomy was carried out on 14th October, 1957. Through a lateral median incision from the pubic symphysis to the umbilicus, the corpus uteri was found to be soft, bluish, and of the size of a goose egg. The cervix and uterine isthmus were distended to the size of a foetal head. A soft myoma, the size of the fist, which filled the Douglas pouch, was found to arise from the cervix and the posterior wall of the uterine isthmus. To comply with the patient's desire to have a baby, conservative treatment was adopted and the incision was closed. The scar healed by granulation, but on the sixteenth post-operative day a partial rupture occurred and a repetition suturing was necessary. There were no uterine contractions during the time that the patient was in hospital. The patient was discharged in good condition on the forty-first post-operative day. The patient was seen fortnightly for clinical examination and was hospitalized for further prenatal investigation at the clinic 8 weeks before term. The examination revealed no disturbance of the pregnancy, but with time the abdominal scar was becoming broader and thinner at the upper end. The patient was re-admitted on 30th January, 1958 (B.C.Nr. 765/58) at 33-weeks gestation. On admission the pulse, temperature and blood pressure were normal. The laboratory tests proved normal, too. The rate of the foetal pulse was 140/minute. The upper pole of the scar was so thin that the abdominal viscera and the uterus could be seen.

On the twelfth day after admission, i.e., at 35-weeks pregnancy, laparotomy was performed because of the danger of rupture of the uterus.

Operative Procedure

The abdomen was opened and the previous scar was removed. The peritoneum was incised at the urethrovesical angle and the bladder was pushed down. The foetal sac rich in blood vessels spread all over its wall was very thin and revealed parts of the foetus, whose movements could be observed. Following a transverse incision of the amniotic sac parallel with the previous peritoneal incision a premature living male infant weighing 2,560 g. was delivered by traction on the lower extremities. The child breathed and cried immediately. After the umbilical cord had been ligated it was noted that the amniotic sac originated in the anterior cervical wall, and that the retroflexed corpus uteri rested on the sac. The myoma of the same size as that of the corpus uteri was seen to grow from the posterior cervical wall; it was located in the Douglas pouch. A thin membranous placenta lined the whole amniotic sac. Total extirpation of the uterus including the distended cervix and the myoma was performed. The left ovary remained. During the operation the patient received 500 ml. of whole blood. Her condition was good.

Post-operative diagnosis: cervical pregnancy at 35-weeks and myoma of the uterus. The post-operative course was good. The patient and the infant were dismissed on the forty-second post-operative day in good condition. At an examination a year later she was found to be well and the child's development was normal.

Gross Post-operative Findings

The uterus measured 20·0 by 8·0 by 8·0 cm. The corpus uteri was found to be enlarged to 8·0 by 8·0 by 8·0 cm. (Figs. 1, 2 and 3). The muscular wall measured 3 to 4 cm. The cavity of the corpus uteri measured 7 cm. It was narrow and was filled with a markedly hypertrophic mucosa. The cervical segment between the isthmus and the vaginal portio was markedly elongated and distended and it measured 19·5 by 18·0 cm. Its posterior wall was 0·7 cm. thick, whilst the anterior wall, distended like a balloon, was only 2 mm. thick. The anterior wall showed a transverse aperture through which the foetus was extracted. This markedly distended cervical canal was filled with the foetal tissue. The main placental mass was attached to the posterior surface above the myoma and at that part it was 4 cm. thick; on the anterior

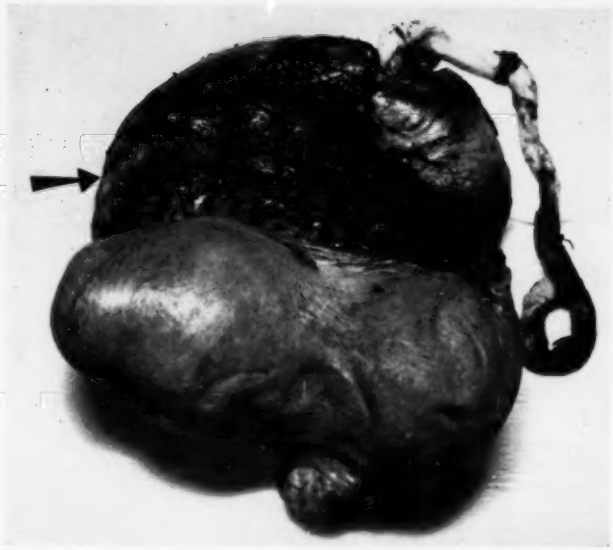

FIG. 1

Above is seen the foetal sac. Below the corpus uteri is on the right, the myoma to the left. The arrow indicates the external os of vaginal portio.

FIG. 2

Section through middle of whole specimen. The entire upper part consists of the foetal sac with the vaginal portio of cervix and the placenta to the right. (There is artefactual separation of placenta from posterior wall of cervix.) In the lower part the myoma is seen to the right and the corpus uteri with hyperplasia of the mucosa to the left.

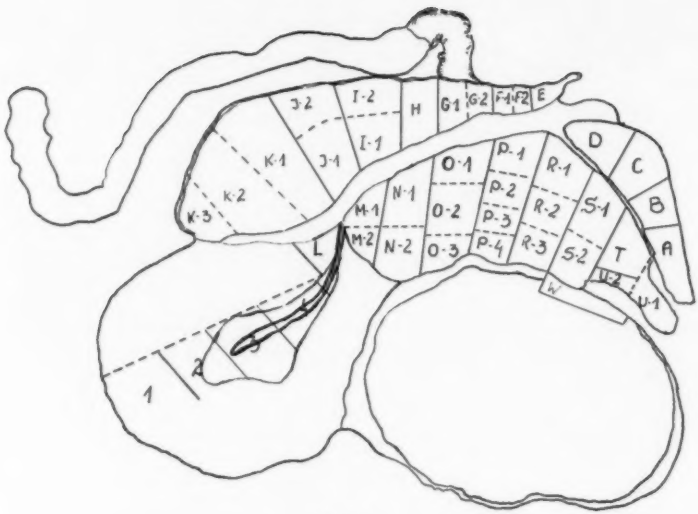

FIG. 3

Shows the location of the specimens removed for histological study. A to U_2 shows placental elements, 1–4 foetal membranes only and W the myoma elements.

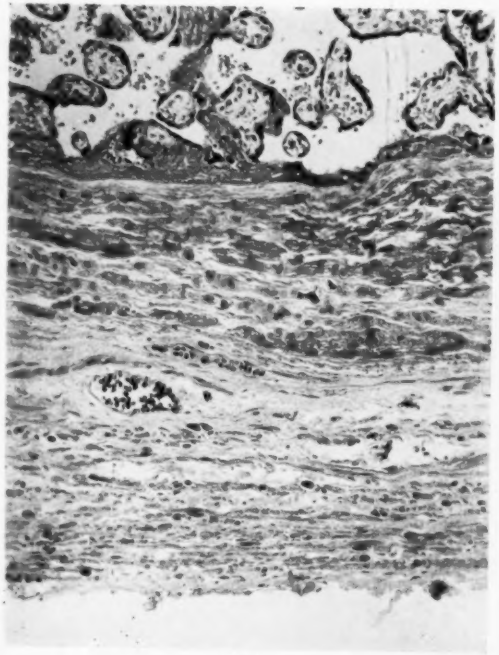

FIG. 4

Specimen E of scheme in Fig. 3: the cervical wall is greatly thinned out and infiltrated by trophoblastic cells. ×205.

FIG. 5

Section U_8 from uterine cervix in Fig. 3, showing placental villi above and cervical gland below. ×205.

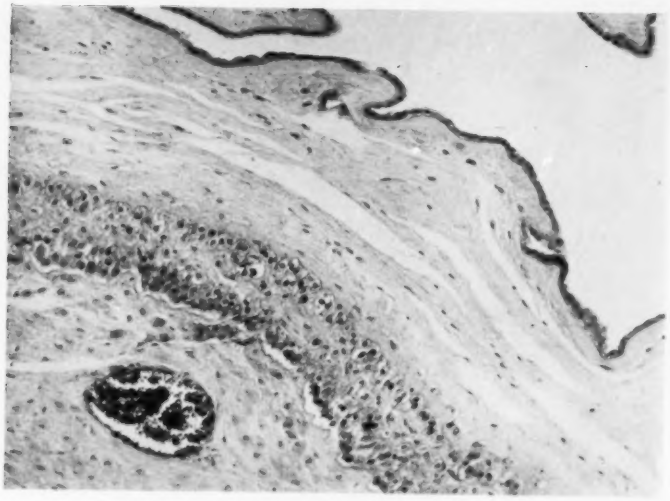

FIG. 6

Specimen from corpus uteri (Fig. 3, 3). Picture showing only foetal membranes: amniotic, chorionic and decidual. ×205.

FIG. 7

Specimen W in Fig. 3. Myoma showing hyaline change and focal necrosis.

wall the placenta was from 2 mm. to 2 cm. thick. With the exception of a small number of white infarcts no pathological placental changes were encountered. The section of the cervix between the lower pole of the foetal sac and the external os measured 1·5 cm. A narrow opening 2 mm. in diameter connecting the amniotic sac with the uterine cavity was revealed above the foetal sac at the site of the isthmus. The amniotic membrane passed through it to line the entire cavity of the corpus uteri. On the posterior cervical wall a sub-serous myoma, elastic and fairly soft and measuring 11·5 by 8·0 by 8·0 cm. was disclosed.

Microscopic Examination

Specimens were taken from the cross-cut surface of the post-operative material and were numbered in sequence (Fig. 3). The wall of the distended part of the cervix is thin, composed in some places of single muscular fibres, fibrous membrane and serous tissue (Fig. 4). Placental elements were revealed in the strips marked A and U_3 of the vaginal portio, i.e., those situated 1·5 cm. from the external to the internal os (Figs. 3 and 5). In the cervical wall of the vaginal portio decidual tissue was present.

The mucous membrane of the corpus uteri was changed into compact and spongy decidua. Placental elements were not present. The entire surface of the decidua was lined only with amniotic membrane and chorion laeve (Fig. 6).

The leiomyoma had become necrotic to a great degree (Fig. 7). Because of the history of pulmonary involvement, the tube, ovary, and parametrium were studied in serial sections: tuberculous lesions were not found.

Discussion

A cervical pregnancy is a pregnancy with the ovum implanted in the mucosa of the cervical canal which does not pass the internal os during its development.

So far, the aetiology of this anomaly is unknown.

The prognosis in cervical pregnancy is bad. In many instances the outcome is grave for the mother and child. Haemorrhages are reported to be violent and profuse. Perforation of the cervix and infection are added risks (Dubuis, 1950). The mortality rate for the mother in cervical pregnancy is 20 per cent according to Schneider, but other authors give a higher percentage, even up to 40–50 per cent (Zangenmeister and Schilling, 1922).

The treatment of cervical pregnancy is exclusively a surgical one. Generally it terminates spontaneously in the early weeks. The youngest cervical pregnancy recognized and reported was at 4-weeks gestation (Marsh and Schuyler, 1953). The most advanced one, at 6-months gestation, was reported by Morton in 1949. In his case the infant measured 32 cm. and was not viable. Cummin (1955) described a cervical pregnancy with a foetus 15·2 cm. long and weighing 226·8 g.

This report presents a case which claims special attention because of the following facts: the cervical pregnancy was carried to 35 weeks and terminated in the birth of a living, normally developed, 2,560 g., male infant. It ended successfully both for mother and child in spite of the laparotomy performed at 14-weeks gestation.

We are not able to answer with certainty the question why the condition did not come to an end at an earlier stage of gestation, and why the pregnancy did not proceed to develop in the corpus uteri.

The possible role of the myoma of the uterine cervix might be twofold:

(1) Localized on the posterior cervical wall it prevented perforation by the placenta of the area most deeply invaded by villi.

(2) By the exertion of pressure on the vaginal portio in the direction of the pubic symphysis the myoma prevented an early escape of the foetus.

Summary

A case of a cervical pregnancy co-existing with a myoma of the uterine cervix in a 36-years old woman is described. The pregnancy terminated at 35-weeks gestation by Caesarean section and extirpation of the entire uterus with the myoma.

The newborn infant is alive and develops normally. The cervical pregnancy was recognized by:

(1) Clinical findings.

(2) Anatomo-histopathological findings:

(*a*) The location of the amniotic sac in the uterine cervix between the vaginal portio and the isthmus.

(*b*) The absence of trophoblastic elements in the corpus uteri.

(*c*) The recognition of the entire vacant corpus uteri with a 7 cm. long cavity beyond the amniotic sac.

From an investigation of the available literature the case herein reported would appear to be the first instance in which a cervical pregnancy has ended in the delivery of an infant capable of developing normally.

Acknowledgments

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SOME OBSERVATIONS ON ANOXIA AS A CAUSE OF DEATH IN THE FOETUS AND NEWBORN

BY

A. E. CLAIREAUX, M.D., F.R.C.P.(Edin.)
Consultant Morbid Anatomist

A. C. FRASER, M.B., B.S., M.R.C.O.G.
Resident Obstetric Officer

AND

W. C. MARSHALL, M.B., B.S.(Sydney), D.C.H.
Resident Paediatric Officer
Queen Charlotte's Maternity Hospital, London, W.6

MATERNAL mortality has been so far reduced that it is no longer an urgent problem. Foetal and perinatal mortality, however, has remained stationary or almost so for some years and it is still a challenge to our efforts. In addition to ensuring that pregnancy is safe we have also to endeavour to see that it is fruitful.

It is always distressing to see on the post-mortem table babies who have died from anoxia somewhere near the time of delivery. These babies are usually quite large and are in all respects normally developed. Their airways have, however, been occluded by meconium. It has also been observed that this particular mode of death would appear to occur more frequently if the pregnancy has progressed beyond term. This does not necessarily mean that all the infants or even a large proportion of them were actually postmature. If a very stringent definition of postmaturity is used such as a gestation period of 44 weeks or over, a birth weight of 4,250 g. or over and a body length of at least 52 cm., then only a comparatively small number of cases could be reviewed.

If, however, we examine all cases in which a pregnancy has lasted beyond 40 weeks it will be seen that an increasing proportion of stillbirths and early neonatal deaths are associated with anoxia.

MATERIAL

During the years 1954–1958 at Queen Charlotte's Maternity Hospital there were 143 perinatal deaths ascribed to anoxia in a total loss of 508 (28 per cent). In 80 cases (16 per cent) anoxia was associated with inhalation of meconium (Table I). It is this group of 80 cases which has received special attention. It was observed that when pregnancy terminated prior to 40 weeks anoxia alone was responsible for the greatest number of perinatal deaths. From 41 weeks onwards, however, anoxia associated with aspiration of meconium became the commonest necropsy finding (Fig. 1).

An analysis of the case histories during the period under review has brought to light some facts which appear to be worthy of note.

Maternal Age

There were 31 multiparous patients in this series, with an average age of 30·45 years. The 49 primiparous patients had ages varying from 17 to 40 years—the average age being 27·56 years.

TABLE I

Perinatal Mortality 1954–58

Weeks	32–37	38	39	40	41	42	43	44+	Total
Anoxia	61	19	14	20	13	12	3	1	143
Anoxia with inhalation of meconium	12	4	7	17	14	16	6	4	80
Congenital abnormalities ..	30	9	7	19	7	2	3	2	79
Birth trauma .. .. .. (subdural haemorrhage)	14	1	2	20	6	5	3	1	52
Haemolytic disease	22	3	1	4	—	—	—	—	30
Hyaline membrane	28	1	—	1	—	—	—	—	30
Atelectasis	5	2	—	1	1	2	—	—	11
Pneumonia	8	—	2	—	—	3	—	—	13
Pulmonary haemorrhage ..	6	1	2	2	—	—	—	—	11
Miscellaneous	8	2	3	10	5	2	3	—	33
Unknown	13	2	3	3	3	1	1	—	26
Total deaths	207	44	41	97	49	43	19	8	508
Total births	1,592	1,481	2,896	4,106	2,583	1,257	405	108	14,428
Total deaths %	13·0	2·9	1·4	2·3	1·9	3·4	4·7	7·4	3·5
Inhalation of meconium % ..	0·75	0·28	0·24	0·41	0·54	1·27	1·48	3·70	0·55

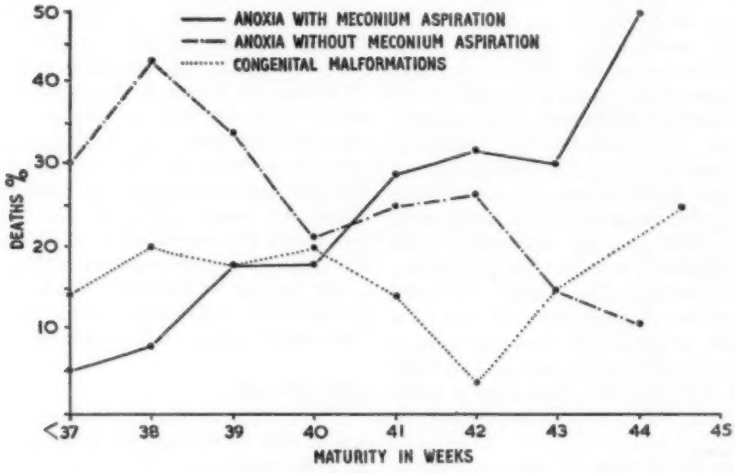

FIG. 1

Incidence of anoxia with aspiration of meconium.

TABLE II

Complications of Pregnancy

	Pre-eclampsia							
Maturity at delivery (weeks)	32–37	38	39	40	41	42	43	44
Total numbers of meconium deaths ..	12	4	7	17	14	16	6	4
Numbers with P.E.T.	5	—	4	6	7	6	2	3
Percentage	41·3	—	57·1	36	50	37·5	33	75

Multiple Pregnancy

There were 6 cases of multiple pregnancy: in 2 cases the first of twins died with anoxia and inhalation of meconium, in 2 cases both sets of twins died and in 1 case the last of triplets died.

Ante-partum Haemorrhage

Two cases of concealed ante-partum haemorrhage occurred. In both cases labour ensued spontaneously and a fresh stillborn foetus was delivered.

Cord Complications

There were 3 cases of prolapsed cord—2 occurring in the only 2 breech presentations in the series. In a further 8 cases, the cord at delivery was recorded as either being tightly around the neck or twice around the neck. In 6 of these cases, however, the foetal heart had become absent before the onset of the 2nd stage of labour and in these cases the position of the cord played little or no part in the anoxic changes found post-mortem.

Toxaemia

There were 19 patients who had a blood pressure of 140/90 mm. Hg or over, together with the presence of albuminuria and oedema and a further 9 patients with a blood pressure of 140/90 in the presence of definite oedema but no albuminuria. Finally, there were 5 patients ho had a raised blood pressure alone, dating om early pregnancy. These 5 patients might be classified separately as Essential Hypertension but as the comparative incidence that will be used is that of Unclassified Toxaemia in the Annual Reports, all 3 categories are grouped together under the heading Toxaemia.

It will thus be seen that 33 cases out of the 80 had one or more symptoms suggestive of toxaemia. This is an incidence of 41 per cent (Table II). This is very much higher than the general incidence of toxaemia in Queen Charlotte's Hospital. In the years 1957 and 1958 there were 814 cases of unclassified toxaemia out of a total of 5,702 deliveries—an incidence of 14·3 per cent.

Out of the 33 cases of toxaemia in the present series, 8 had labour induced because of increasing severity of the symptoms. The remainder improved with rest and treatment and labour was allowed to commence spontaneously.

Onset of Labour

In 69 cases, labour commenced spontaneously, in the remaining 11 labour was induced by means of artificial rupture of the membranes in 9 and by use of a pitocin transfusion in 2. The reasons given for induction were toxaemia in 7 cases and postmaturity in 4. In 6 of the 9 cases induced surgically there was an induction-delivery interval of over 70 hours (Table III).

Duration of Labour

Ten primiparae had a 1st stage of over 24-hours duration and a further 8 had a 1st stage

TABLE III
Onset of Labour

Maturity (weeks)	32–37	38	39	40	41	42	43	44
Spontaneous	10	4	6	15	13	13	6	2
Induction	P.E.T. 2	—	P.E.T. 1	P.E.T. 2	P.E.T. 2	Post-maturity 2	—	Post-maturity 2

of over 48-hours duration (Table IV). Of the multiparous patients in the series only 3 had a 1st stage of over 24 hours.

State of Liquor

In a large number of cases the state of the liquor has not been recorded, especially where the membranes ruptured before admission. Nevertheless it must be assumed that in the majority meconium-staining first appeared during the 2nd stage of labour and was not recorded.

In only 8 cases was the liquor definitely recorded as being clear throughout labour. In a further 17 the liquor was meconium-stained from the time of rupture of the membranes. In 11 of these cases this occurred during the 1st stage and the foetal heart was already absent in 5 of them.

There were a further 15 cases where the liquor became meconium-stained after rupture of the membranes. All but 1 were primiparous patients and in each case meconium appeared during the 1st stage of labour. In only 1 of these

TABLE IV
Duration of Labour

	Primiparae						
	1st Stage			2nd Stage			
	0–23 Hours	24–48 Hours	Over 48 Hours	<5 Minutes	5 Minutes–1 Hour	1–2 Hours	Over 2 Hours
S.V.D. ..	28	3	3	4	18	10	2
Forceps ..	3	7	3	–	5	3	5
Breech ..	—	—	–	–	—	—	–
L.S.C.S. ..	—	—	2	–	—	—	–
	31	10	8	4	23	13	7

TABLE V

State of Liquor Amnii

Weeks	32–37	38	39	40	41	42	43	44	Total
Clear liquor when membranes ruptured. Remained clear	1	–	2	3	–	2	–	–	8
Meconium-stained liquor when membranes ruptured	1	–	2	4	5	3	2	–	17
Clear liquor becoming meconium-stained before delivery	–	–	1	4	1	4	3	2	15
Meconium-stained at delivery	1	–	–	1	1	1	1	1	6
Unknown	9	4	2	5	7	6	–	1	34

Duration of Rupture of Membranes

48 hours or longer	12 cases
24–48 hours	6 cases
12–23 hours	3 cases
6–11 hours	7 cases
1– 5 hours	6 cases
0– 1 hour	14 cases
Not known	32 cases

cases was the foetal heart absent before the appearance of meconium.

Finally there were 6 cases where meconium-stained liquor was first noted at delivery and although in 3 of these cases the foetal heart was reported as being satisfactory throughout the 2nd stage, only one of the infants was born alive (Table V).

The Foetal Heart

Table VI shows the foetal heart recordings in these 80 cases. The striking feature here is the large number of cases where the foetal heart became absent suddenly without any warning signs of a fall or increase in the heart rate.

In 8 cases there were some warning changes in the foetal heart rate before it became absent. Three of these cases occurred during the 1st stage of labour and were associated with an increase in the foetal heart rate. The other 5 cases occurred in the 2nd stage and in each case there was a slowing of the heart rate.

There were 12 cases where the foetal heart rate was recorded as satisfactory throughout labour and all the neonatal deaths occurred in this group.

TABLE VI

Meconium Stained Liquor in Relationship to Foetal Heart Chart

	Cases
1. Foetal heart absent before onset of labour	29
2. Foetal heart becoming absent *suddenly* during labour:	
Before appearance of meconium	6
With appearance of meconium	6
After appearance of meconium	8
Without appearance of meconium	7
Total	27
3. Foetal heart becoming absent after *irregularity* during labour:	
Before appearance of meconium	1
With appearance of meconium	3
After appearance of meconium	1
Without recorded meconium	3
Total	8
4. Foetal heart *satisfactory*:	
With meconium before delivery	4
With meconium at delivery	4
Without recorded meconium	4
Total	12
5. Born before arrival	4

TABLE VII
Outcome of Labour

Maturity (weeks)	32–37	38	39	40	41	42	43	44	Total
Spontaneous vertex delivery ..	11	3	6	14	11	11	2	3	61
Forceps	1	–	1	1	2	5	4	1	15
Section	—	–	–	2	—	—	–	–	2
Breech	—	1	–	—	1	—	–	–	2

15 cases of forceps delivery (19 per cent)

Delay in second stage ..	8
Foetal distress	3
Uterine inertia	3
Multiple pregnancy ..	1

Method of Delivery

There was a spontaneous vertex delivery in 61 cases. Delivery was effected by forceps in 15 cases. The infant was delivered as a breech on 2 occasions. There were 2 Caesarean sections for prolonged labour; in both cases meconium-stained liquor was present but the foetal heart remained satisfactory, the infants dying soon after delivery.

The main reason for interference in the forceps deliveries was delay in the 2nd stage with the foetus already dead; in fact only 3 out of the 15 forceps deliveries were done for foetal distress (Table VII).

Neonatal Deaths

The 8 live-born infants in this series died shortly after delivery from the effects of inhalation of meconium. The obstetric history did not differ materially from that of the other 72 cases. Three patients gave a history of pre-eclamptic toxaemia lasting 1 week or more.

Gestation by dates was 40 weeks in 6 cases and the other 2 were 42 and 43 weeks respectively. This estimate was supported by the weight of these infants; one weighed 2,949 g. and the remainder were over 3,000 g., the heaviest being 4,833 g.

In 4 of the cases, meconium-staining of the liquor was present for 5–6 hours before delivery and in 3 cases it was only noted at birth. In the remaining case the liquor was recorded as being "purulent" following artificial rupture of the membranes 4 days prior to delivery. The foetal heart was recorded as normal during labour in all cases except one where the rate fell below 110 beats per minute for a short period during the 2nd stage and then became normal.

There was a spontaneous vertex delivery in 4 cases. Two infants were delivered by lower segment Caesarean section and the other 2 by forceps because of deep transverse arrest.

Respiratory distress in the form of cyanosis, apnoea or irregular gasping respirations with retraction of the soft parts occurred within a few minutes of delivery in 7 of these infants. The respirations of the remaining infant became laboured after about 2 hours of apparently normal respiratory movements, and coarse crepitations were heard in the chest. Death occurred within 40 minutes of delivery in 4 infants, whilst 2 survived 2 hours and the remainder 18 and 34 hours respectively.

PATHOLOGICAL FINDINGS

These babies are usually large and a number of them would appear to be postmature. Their skin is covered with meconium and their umbilical cords are bright green in colour. The foetal surface of the placenta is also green.

At post-mortem there appear to be two forms of meconium aspiration. Firstly, there is a block of the major airways—trachea and large bronchi,

by plugs of meconium. The lungs in such cases are collapsed and for all practical purposes are unexpansible. Secondly, the infant appears to have aspirated *in utero* an emulsion of meconium and liquor amnii. This enables the former to reach the farthest intra-pulmonary bronchi and even alveolar ducts and alveoli. The lungs are voluminous, but contain no air and on slicing are often dark green in colour. This is the appearance of a massive aspiration of meconium. Apart from the meconium the lungs are often covered by innumerable small subpleural petechial haemorrhages. These signs of anoxia may also be present over the heart, the thymus and in the brain.

On histological examination meconium shows as an amorphous acidophil or bile stained debris in which many squames are enmeshed (Figs. 2 and 3). In a few cases squames and liquor debris lie in a thin mucous web of meconium (Fig. 4). The lungs are intensely engorged and subpleural, interstitial and even intra-alveolar haemorrhage may be present (Fig. 5). The brain may also be involved in the general anoxic pattern and small petechial haemorrhages may be found (Fig. 6). These latter lesions are of some importance as there is always the possibility of late neurological damage in infants who manage to survive beyond the neonatal period.

That is the picture in the stillbirth. The infant who aspirates meconium prior to delivery but is still alive at birth has to run additional hazards. The meconium aspirated may act as a partial block to respiration. Indeed at times it appears to have a ball-valve action which allows air in but interferes with expiration. This leads to the development of interstitial and subpleural emphysema (Fig. 7). Bullae are formed beneath the pleura and may rupture with the consequent development of a pneumothorax. In other infants the air tracks backwards along the bronchovascular spaces and a mediastinal emphysema develops. In these patients the thymus may be sitting up on a bubble of air.

Another hazard in the newborn is the development of pneumonia. The poorly aerated, half expanded lung partially blocked by meconium is liable to bacterial invasion and these infants are very susceptible to pulmonary infections. In other infants the lungs are already consolidated at delivery and, on histological examination, have an apparent pneumonic condition. This is the so-called intra-uterine pneumonia. The exudate is chiefly in alveoli and alveolar ducts and is composed of polymorphonuclear leucocytes and histiocytes (Fig. 8). It contains no fibrin and the bronchioles appear to be less affected than in the classical broncho-pneumonia of the neonatal period. Furthermore, the bacterial nature of this so-called infection is open to doubt. Over a period of a year we carried out bacteriological investigations into all these cases but only in a few instances were organisms isolated. In the vast majority of cases the cultures were sterile although the histological appearances were similar to those in proved cases of respiratory infection.

One further point should perhaps be mentioned at this stage. In no less than one-third of infants dying from birth trauma who are delivered after 41 weeks or longer, there is evidence of anoxic changes and aspiration of meconium. This may account for the not infrequent finding of subdural haemorrhage at necropsy in an infant who has been delivered by "easy" forceps. These infants have such intense cerebral venous engorgement that minimal trauma which would have little effect in a normal infant is sufficient to cause a fatal intracranial bleeding.

Discussion

A survey of these 80 infants who died as a result of anoxia associated with inhalation of meconium reveals a number of interesting features.

The clinical picture is that of a patient with a large baby, often a few weeks overdue, who has meconium-staining of the liquor during labour. The foetal heart sounds may disappear suddenly during labour and the only findings at necropsy are those described above.

A high incidence of toxaemia of pregnancy (41 per cent) was noted among the patients in this series. It is tempting to suggest that foetal loss might be lower if patients with toxaemia were not allowed to go beyond term. Many of these patients improve clinically with bed rest and sedation. Their blood pressure falls and the

albuminuria and oedema may disappear. Unfortunately, this improvement in the mother's condition is not necessarily reflected in the stillbirth and neonatal death rate. The latter still tends to be high in spite of the disappearance of toxaemic symptoms.

The majority of the infants in this series were stillborn. It is noteworthy that the 8 infants who survived for a short period after delivery were not exposed to meconium-stained liquor for more than 6 hours before birth. The shorter the period the infant is bathed in this liquor probably means the shorter the time it is suffering from anoxia and the greater the chance of survival. The appearance of meconium-stained liquor during labour, especially if the pregnancy has gone beyond term, is an ominous sign. A number of workers have commented on its significance.

Clifford (1954) examined a series of infants who were delivered after term and had "yellow vernix". These infants did not suffer from haemolytic disease. The author defined postmaturity as a pregnancy lasting over 300 days and stated that this occurs in about 6 per cent of all pregnancies. As in our series, Clifford found that postmaturity was a particular hazard of the primigravida. Furthermore, 85 per cent of the foetal loss associated with postmaturity takes place *prior* to delivery.

Since postmaturity is common (6 per cent of all pregnancies) the author suggests that placental dysfunction is responsible for the foetal loss. He stresses the danger to primigravidae and in his series 73 per cent of them had no further children. He suggests that the placenta might undergo premature senility in these cases.

Arey and Dent (1953) studied a group of 137 perinatal deaths. There were 102 neonatal deaths and 35 fresh stillbirths in their series. Aspiration of amniotic sac content (including meconium) was held responsible for 10 per cent of the neonatal deaths and 33 per cent of the stillbirths.

Desmond, Moore, Lindsey and Brown (1957) regarded meconium-staining of the liquor amnii as a sign of foetal distress in cephalic presentations. In a series of 3,965 deliveries there were 407 (10·9 per cent) in which meconium-staining of the amniotic fluid was noted. There were 408 infants in this series and 96·4 per cent were at least mature. Three hundred and sixteen had no difficulty with respiration but 93 had initial respiratory difficulty and 15 died (3·75 per cent). Two-thirds of the babies were stained with meconium. Toxaemia of pregnancy was found twice as frequently in the patients in their series as in a control group. Postmaturity was also twice as common compared with controls and 27 mothers had a gestation period of over 42 weeks. In 15 cases hypertension or diabetes or anaemia was found as well as postmaturity. The frequency of meconium-staining of the liquor amnii was higher than in the series reported by Schultze (1925) who found it in 3 per cent of his cases, McCall and Fulsher (1953) who put the figure at 0·5 per cent and White (1955) who found it in 5 per cent of his material. In our hospital the incidence is about 15 per cent. At term the oxygen saturation of a normal foetus is about 60 per cent. Walker (1954) suggested that meconium is passed into the liquor when the oxygen saturation in the umbilical vein falls to 30 per cent. There is still no clear explanation of the circumstances under which meconium is passed into the liquor. Anoxia is thought to cause increased peristalsis of the intestinal tract and later relaxation of the sphincter ani.

It is clear, therefore, that meconium staining of the liquor may be a danger sign in infants presenting by the vertex but there is still a lack of precise criteria for rapid intervention to save the foetus.

If an infant weighing more than 3,000 g. at birth has respiratory difficulty soon after delivery and there is a history of meconium-staining of the liquor, aspiration of meconium should be suspected. If meconium is aspirated from the larynx or trachea in such a case the main airway can be cleared but the bronchi may be blocked lower down. Once meconium is aspirated into the lower bronchi no amount of sucking out will be effective. If only a single plug of meconium has passed into the bronchi, the latter may be cleared *via* a bronchoscope.

Radiographic changes in the lungs of postmature infants have been described by Currarino and Silverman (1957). The findings are similar to those seen in connexion with aspiration of

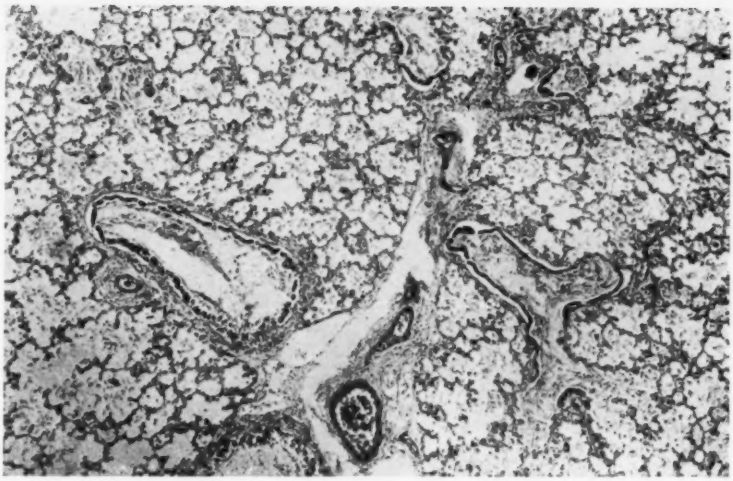

FIG. 2

Lung. Plugs of meconium debris in medium and terminal bronchi. H. & E. ×88.

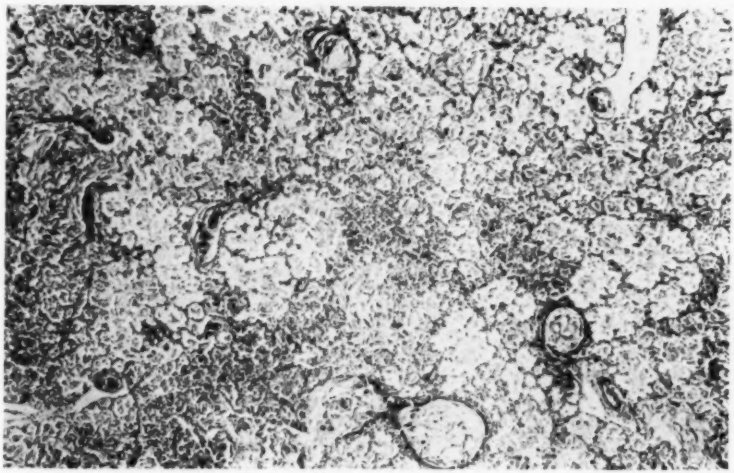

FIG. 3

Lung. Plugs of meconium in bronchioles. Numerous squames and debris in alveolar ducts and alveoli. H. & E. ×88.

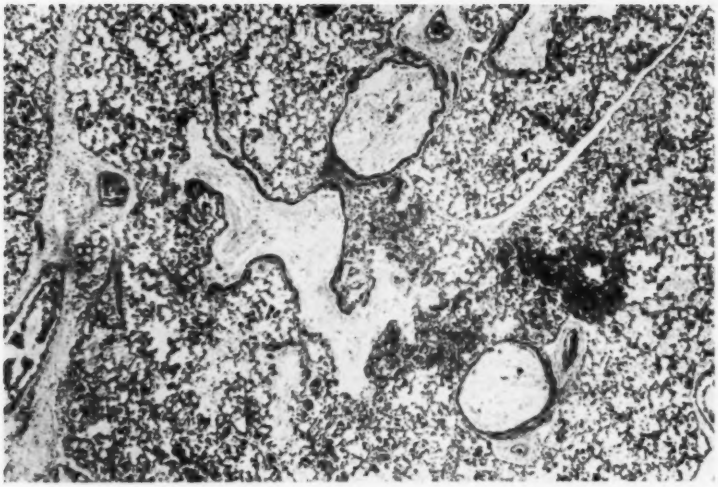

FIG. 4

Lung. Plugs of meconium in terminal bronchioles. Some haemorrhage is also present. H. & E. ×73.

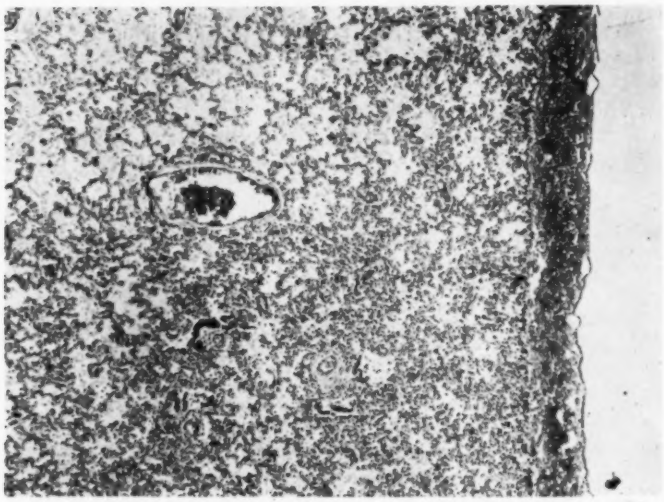

FIG. 5

Lung. Extensive subpleural haemorrhage. H. & E. ×73.

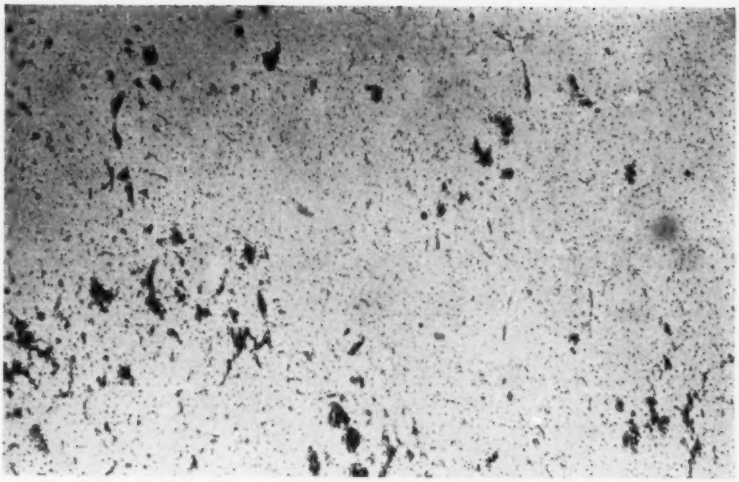

FIG. 6

Brain. Numerous small perivascular haemorrhages. H. & E. ×73.

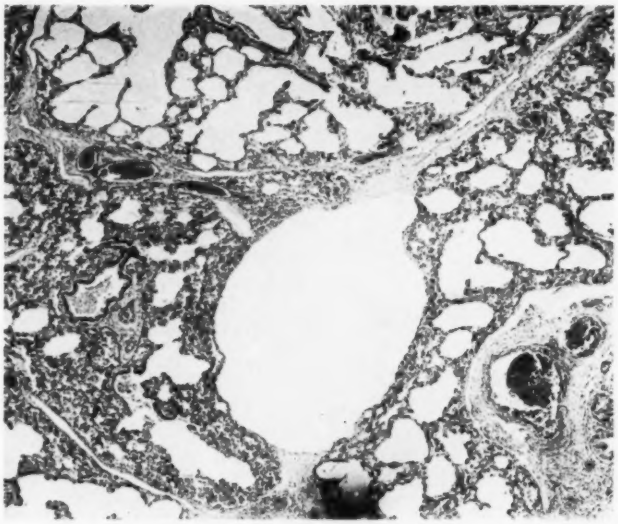

FIG. 7

Lung. Interstitial emphysema. H. & E. ×74.

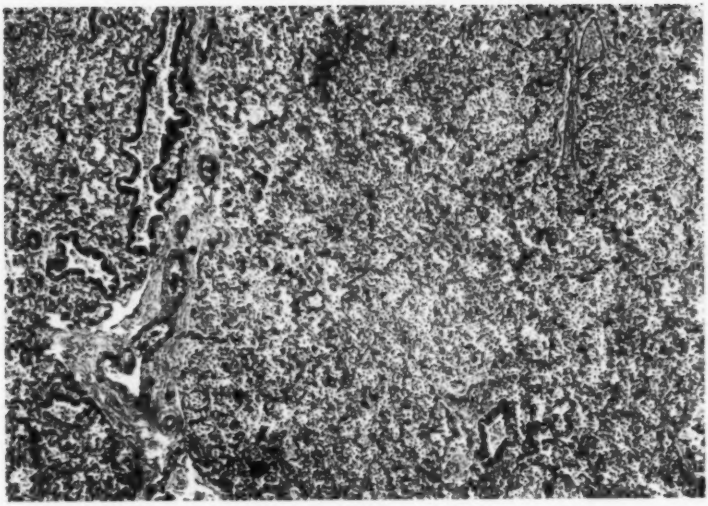

FIG. 8

Lung. Intra-uterine pneumonia. H. & E. ×87.

any foreign material. The thoracic cage becomes over-expanded, the diaphragm flattened and the sternum elevated. Irregular, coarse lung markings extend outwards from the hilar region and there may be zones of generalized emphysema with scattered areas of lobular, segmental collapse. If the infant should survive for some time after birth, there may be superimposed inflammatory changes. It is thus clear that the newborn infant who has aspirated large quantities of meconium is seriously handicapped in its efforts to sustain extra-uterine life. There is also the danger that a forceps delivery of a baby suffering from severe anoxia with meconium-aspiration may result in a fatal intracranial haemorrhage even although the delivery itself would appear to have been without trauma.

Even should the infant survive the hazards of a stormy neonatal period there is the danger that cerebral damage may have occurred during the period of anoxia at the time of delivery. Small anoxic haemorrhages may occur in the cerebral parenchyma (Claireaux, 1959) and less severe lesions may not be fatal. The affected infant may later suffer from cerebral palsy and exhibit spasticity or athetosis.

It is, therefore, important to try to reduce the foetal loss from anoxia and to prevent the foetus from being exposed to oxygen lack for prolonged periods during delivery. The risk to the foetus when pregnancy proceeds beyond term has been noted by Gibberd (1958) who is also careful to point out that routine induction of labour in such cases may be even more hazardous since there is as yet no infallible method of induction. The danger seems to be much greater for the primigravida than in the multiparous patient. The combination of primiparity, toxaemia, postmaturity and meconium-staining of the liquor at delivery is to be avoided if at all possible.

Summary

(1) The clinical and pathological features in 80 cases of foetal anoxia associated with aspiration of meconium are described.

(2) This particular mode of death would appear to be commoner in the offspring of primigravidae.

(3) Toxaemia and postmaturity are associated factors.

(4) The foetal heart sounds are liable to disappear suddenly and no warning irregularity may be noted.

(5) Even if the infant survives delivery it is liable to develop emphysema or pneumonia or both.

(6) The significance of meconium-stained liquor is discussed.

Acknowledgments

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MATERNAL AND OBSTETRIC FACTORS IN ASPHYXIA NEONATORUM WITH A PRELIMINARY REPORT ON A POSSIBLE ASSOCIATION WITH ABO BLOOD GROUPS

BY

GERALD J. AMIEL, M.B., M.R.C.O.G.
Consultant Obstetrician and Gynaecologist
Bromley Group of Hospitals, Kent

INTRODUCTION

ALTHOUGH in the past decade there has been a marked fall in the Infant Mortality Rate, progress in the prevention of stillbirths and deaths of infants in the first week of life has been disappointingly small. This relatively small reduction in the perinatal mortality rate is shown in Table I compiled from the Registrar-General's (1958) return.

In the study that follows it is shown that asphyxia neonatorum and the effects of anoxia play a major role in perinatal mortality and a detailed analysis is made of factors predisposing to the condition. The case records of 5,169 consecutive deliveries conducted in a modern maternity hospital, and under unchanged clinical supervision, have been studied and 16 maternal or obstetric factors analyzed. The analysis is summarized in a series of tables. From these tables deductions point to certain trends and these are compared and contrasted with those in modern obstetric practice.

TABLE I

	1947	1956	Percentage Reduction
Infant mortality	41·4	23·7	42·8
Neonatal mortality	22·7	16·8	26·0
Perinatal mortality	40·2	36·8	8·5
Stillbirth	24·1	22·9	5·0
Infant deaths under one week	16·1	13·9	13·7

Infant mortality rate—Deaths of infants under 1 year of age per 1,000 live births.

Neonatal mortality rate—Deaths of infants under 4 weeks of age per 1,000 live births.

Perinatal mortality rate—Deaths of infants under 1 week and stillbirths per 1,000 total births.

The calculation of the exact foetal risk as a percentage in any one factor, gives what may be termed the "asphyxia index" for that factor. The knowledge of this will assist in the elimination of asphyxia neonatorum, or, where a factor with a high asphyxial index is unavoidable, preparedness for the condition will aid in mitigating the effects.

In England and Wales, in 1955, 31 per cent of all infant deaths occurred in the first day of life (Ministry of Health, 1957). In the United States of America "nearly 40,000 infants fail to survive the first 24 hours of life" (Maeder, 1957). The majority of these deaths are associated with asphyxia and few would disagree with Smith and Cook (1955) who state that "ventilatory difficulty accounts for approximately 50 per cent of neonatal mortality". The morbidity that may result from anoxia at birth, manifest perhaps by mental retardation, spasticity or epilepsy, is incalculable. It is considered that this study may not only contribute towards reducing this morbidity, but may also be a contribution towards the reduction of perinatal mortality.

Terminology and Importance of Asphyxia Neonatorum

Asphyxia literally means "stoppage of the pulse" and many authors have stated that the term to describe a failure of normal respiration should be "apnoea neonatorum" rather than "asphyxia neonatorum". DeLee and Greenhill (1947) agree with Eastman (1936) who used the term "asphyxia neonatorum" to mean failure of an infant to breathe at birth because of an inadequate supply of oxygen during labour, and "apnoea neonatorum" to indicate failure of respiration from unknown or combined causes (cerebral haemorrhage and congenital defects). However, initially it is often impossible to distinguish between these two, and in this survey the term asphyxia, because of prolonged and common usage, is taken to mean any failure of normal respiration. This failure will always result in a condition of hypoxia or anoxia.

The length of time after birth in which the term "neonatorum" may be used in this connexion appears to be capable of wide variation. Russ (1953) states that "the presence of neonatal apnoea may be stated to exist whenever the baby has failed to take a spontaneous respiratory movement within 30 seconds of severing the cord". After this time it "becomes imperative to initiate interference in order to ensure adequate oxygenation so that cerebral damage might be prevented". Blaikley (1956) however quotes a case of infant survival after 45 minutes of complete rupture of the cord and feels that there is a tendency to exaggerate the risks of short periods of oxygen lack, but adds "none the less we are right in trying to avoid unnecessary prolongation of anoxia". Yohe (1958) states that 5–10 minutes is considered a safe time to await active respirations. In this study any baby which had failed to establish and maintain normal breathing within 5 minutes of delivery of the head and in which it was deemed advisable to administer pure oxygen, has been considered to have had asphyxia neonatorum. If other signs were present, especially those of "shock", this interval of 5 minutes may have been shortened.

Furthermore in the tables the cases of asphyxia neonatorum have been subdivided, using the old classification of livida and pallida, the most significant feature of the latter being vasomotor collapse. Although this classification has been condemned by Russ (1953) as "quite outmoded" it differs but little from that which he considers the best, and advocated by Flagg whose clinical classification divided the cases into mild, moderate and severe. Russ states "it has been my experience, augmented by experiences of others, that many cases of asphyxia livida are even more severely shocked and closer to death than those presenting asphyxia pallida". The fact that an asphyxiated baby is severely shocked is in itself enough to classify the asphyxia as of the pallid type and in this survey such a case is so typed. Asphyxia neonatorum is not a clinical sign—it is a clinical state.

Gibberd (1947) points out that the two types, livida and pallida, are really different stages in progressive anoxaemia, one being "the beginning and the other the end". That the "end" of progressive anoxaemia is foetal death is shown by the same author (Gibberd, 1958) when he states that the ill effects of anoxia could be manifest in three ways as follows:

(1) *Prenatal Death*

"If we take a group containing all the cases of macerated foetus in which there was no maternal disease—e.g., toxaemia and diabetes—nor any foetal abnormality, e.g., retroplacental haematoma and hydrops foetalis—we shall have a group which will contain all the ante-partum deaths due to the anoxia of placental insufficiency."

(2) *Intranatal Death*

"The anoxia due to placental insufficiency might conceivably be of an order that did not kill the foetus until the anoxia of labour were added. In such a case the foetus might die during labour, and necropsy would not reveal any abnormality apart from the signs of asphyxia; nor would a review of the clinical course of labour show any mechanical accident to account for the fatal anoxia."

(3) *Postnatal Death*

"The anoxia due to placental insufficiency might be even less than in the former group and cause only a severe intranatal asphyxia, with the

result that the infant is born alive in a more or less drowned state of 'asphyxia neonatorum', only to die within a few minutes or days because of non-aeration of its lungs."

Thus it may be seen how the ill effects of anoxia, depending upon magnitude and time of occurrence, may cause either asphyxia neonatorum possibly with neonatal death, fresh stillbirth or maceration.

In 100 consecutive cases of neonatal asphyxia, there were only 29 in which there were signs of foetal distress, as evidenced by foetal heart changes and/or the passage of meconium prior to delivery. Lister and Buchanan (1957), too, found that in more than half of the asphyxiated babies in their series there had been no evidence of foetal distress.

It is an indisputable fact that asphyxia neonatorum and the effects of anoxia play a major role in perinatal mortality. By the use of the tables that follow, the risk of a baby suffering from asphyxia neonatorum may be mathematically calculated in the circumstances that have been considered.

Of the 510 affected babies reviewed in the survey, 335 of 348 (96·3 per cent) survived blue asphyxia and 141 of 162 (87·0 per cent) lived after white asphyxia. The high survival rate must be partly due to resuscitation. Therefore, when the risks of an asphyxiated infant being delivered are high from a study of the tables, the means of resuscitation must be immediately available. The tables, too, may be of assistance in determining the duration of a trial of labour. The fact emerges, for example, that even though the danger of asphyxia is greater as the duration of the first stage of labour increases, there is less foetal risk in allowing a woman with blood group O to have a first stage of from 12–24 hours, than there is in permitting a first stage of from 0–12 hours, in a patient with blood group A.

Survey Results

The annual totals of the deliveries are shown in Table II and the detailed analysis of the various factors studied are summarized in Tables III to X.

Other factors investigated included maternal age, parity and drugs administered during labour. The conclusions drawn were found to correspond with accepted teaching and these tables have been omitted.

In Table VIII it may be seen that when pregnancy is complicated by pre-eclamptic toxaemia the incidence of asphyxia neonatorum is increased from 8·7 to 20·3 per cent, i.e., by 133·3 per cent. In the third, fourth and fifth columns of this table, the three classical features of the disease, namely hypertension, oedema and albuminuria, have been separately assessed and it may be seen that the highest percentage of asphyxiated babies is found in association with albuminuria. The diagnosis of essential hypertension was made only when the blood pressure was elevated above 140/90 mm. of mercury at the first visit and subsequently

Table II

Annual Totals of the Deliveries

	Total Deliveries	Normal Infants	Infants with Blue Asphyxia	Infants with White Asphyxia	Stillbirths
1953	998	873	52	55	18
1954	977	841	83	38	15
1955	1,008	897	76	24	11
1956	1,055	955	64	21	15
1957	1,131	1,018	73	24	16
Grand total	5,169	4,584	348	162	75
Percentage of total deliveries ..	100	88·7	6·7	3·1	1·5

TABLE III

	Maturity							
	Weeks			38 Weeks to Term+ 4 Days	Days Postmature			
	Less than 32	32–36	36–38		5–10	11–16	17–22	23+
Normal	12	62	268	2,589	911	566	158	18
Blue asphyxia ..	12	18	26	159	65	48	15	5
White asphyxia ..	9	11	11	57	31	28	7	8
Stillborn	19	18	7	22	3	3	2	1
Total births ..	52	109	312	2,827	1,010	645	182	32
Asphyxia—per cent	40·4	26·6	11·9	7·6	9·5	11·8	12·1	40·6

TABLE IV

	Foetal Position at Delivery				Mode of Delivery			
	Occipito-Anterior	Persistent Occipito-Posterior	Breech	Other	Spontaneous	Forceps Extraction	Caesarean Section	Breech Extraction
Normal	4,364	113	81	26	4,344	138	86	16
Blue asphyxia ..	295	16	28	9	255	55	30	8
White asphyxia ..	133	13	12	4	123	24	11	4
Stillborn	40	3	19	13	64	6	2	3
Total births ..	4,832	145	140	52	4,786	223	129	31
Asphyxia—per cent	8·9	20·0	28·6	25·0	7·9	35·4	31·8	38·7

TABLE V

	Engagement of Head					Rupture of Membranes	
	?	Not Before Labour	Weeks Before Labour			Before Labour	After Labour
			0–2	2–4	4+		
Normal	790	1,225	496	562	1,404	1,267	3,317
Blue asphyxia	52	141	27	25	66	126	222
White asphyxia ..	30	68	10	11	27	61	101
Stillborn	6	26	2	2	7	34	41
Total births	878	1,460	535	600	1,504	1,488	3,681
Asphyxia—per cent ..	9·3	14·3	6·9	6·0	6·2	12·6	8·8

TABLE VI

	Duration of Labour								
	First Stage					Second Stage			
	Less than 12 Hours	12–24 Hours	24–36 Hours	36–48 Hours	48+ Hours	10 Minutes or Less	10 Minutes to 1 Hour	1–2 Hours	2+ Hours
Normal	2,708	1,303	322	113	76	639	2,572	931	356
Blue asphyxia	189	83	31	22	13	21	164	72	63
White asphyxia	79	47	16	5	12	21	60	32	39
Stillborn	52	15	2	3	1	27	34	10	2
Total births	3,028	1,448	371	143	102	708	2,830	1,045	460
Asphyxia—per cent	8·8	9·0	12·7	18·9	24·5	5·9	7·9	10·0	22·2

TABLE VII

	Blood Group									
	A	B	AB	O	?	Rh Positive	Rh Negative	Husbands of Rh− Wives		
								Rh+	Rh−	?
Normal	1,963	393	131	2,065	32	3,775	777	608	135	34
Blue asphyxia ..	158	30	11	143	6	290	52	42	7	3
White asphyxia ..	76	14	1	66	5	132	25	18	4	3
Stillborn	27	6	3	34	5	65	5	2	2	1
Total births ..	2,224	443	146	2,308	48	4,262	859	670	148	41
Asphyxia—per cent	10·5	9·9	8·2	9·1	—	9·9	9·0	9·0	7·4	—

TABLE VIII

	Toxaemia					
	Nil	Pre-eclamptic Toxaemia	Hypertension	Oedema	Albuminuria	Essential Hypertension
Normal	4,201	383	373	251	148	26
Blue asphyxia ..	272	76	72	51	33	1
White asphyxia ..	136	26	26	16	12	1
Stillborn	57	18	16	8	12	1
Total births ..	4,666	503	487	326	205	29
Asphyxia—per cent	8·7	20·3	20·1	20·6	22·0	6·9

TABLE IX

	Induction of Labour				
	Method		Indication		
	Medical	Surgical	Pre-eclamptic Toxaemia	Postmaturity	Other
Normal	154	389	183	332	72
Blue asphyxia	6	65	38	31	8
White asphyxia	10	20	13	13	3
Stillborn	3	26	4	2	25
Total births	173	500	238	378	108
Asphyxia—per cent	9·2	17·0	21·4	11·6	10·2

TABLE X

Miscellaneous Factors

	Emergency Admissions	Ante-partum Haemorrhage	Gross Congenital Abnormalities	Contracted Pelvis	Twins	External Cephalic Version	Maternal Heart or Lung Disease	Neonatal Death
Normal ..	99	84	21	48	102	500	42	10
Blue asphyxia ..	17	23	4	14	27	34	3	13
White asphyxia	12	12	12	3	10	22	1	21
Stillborn ..	10	9	16	3	5	9	0	—
Total births ..	138	128	53	68	144	565	46	44
Asphyxia—(%)	21·0	27·3	30·2	25·0	25·7	9·9	8·7	71·3

remained higher. This restricted use of the term has resulted in the number of cases being too small to be statistically significant.

A study of the tables shows that under ideal conditions which are:

Normal maturity	7·6 per cent
Occipito-anterior position	8·9 per cent
Head engaged before labour	6·0–6·9 per cent
Membranes intact at onset of labour	8·8 per cent
First stage of labour under 24 hours	9·0 per cent
Second stage of labour under 1 hour	7·9 per cent

the foetal risk never exceeds 9·0 per cent. This figure may thus be considered the basic risk and any appreciable rise is to be avoided if possible.

The important risks, in order, are shown to be:

(1) 23 or more days post-maturity	40·6 per cent
(2) Pregnancy lasting 32 weeks or less	40·4 per cent
(3) Breech extraction	38·7 per cent
(4) Forceps extraction	35·4 per cent
(5) Caesarean section	31·8 per cent
(6) Congenital abnormalities	30·2 per cent
(7) Breech presentation at delivery	28·6 per cent
(8) Ante-partum haemorrhage	27·3 per cent
(9) 32–36 weeks maturity	26·6 per cent
(10) Twin pregnancy	25·7 per cent

Some of the more controversial and interesting facts that emerge from the study are now considered in more detail.

Postmaturity and Induction of Labour

The vast majority of estimates on the duration of pregnancy were obtained from the menstrual history. The method used was that of adding one year and seven days to the first day of the last menstrual period and counting back three months. Where the patient was in doubt regarding menstrual history, the size of the uterus at the first visit coupled subsequently with the time when foetal movements were first felt, were used in arriving at an estimated day of delivery. Even though both these methods are only approximate, in every case a day was named before labour commenced, and that date has been utilized in the survey.

The tables show that the two most potent factors in causing asphyxia neonatorum are, firstly, postmaturity of more than 23 days, and next, prematurity where pregnancy had lasted under 32 weeks. The fact that prematurity is a most important factor in asphyxia and stillbirth is of course universally established, but this survey shows that postmaturity of more than 23 days is an even greater hazard and this needs further examination.

Since Ballantyne and Browne (1922) stated that "postmaturity of the foetus is a condition that has real existence" much controversy has raged about the topic. Most writers however agree that there is an increased foetal risk associated with prolonged pregnancy. Clayton (1941) associated the increased mortality with ordinary obstetric hazards. Higgins (1956) felt that hypertension and dystocia were more common in prolonged pregnancy and Martin (1955) too had written of the importance of hypertension. Nesbitt (1956), reviewing cases in Johns Hopkins Hospital where pregnancy had lasted 294 days or more, found a threefold increase in the postmature perinatal mortality rate, the most marked feature being foetal death occurring in labour. Walker (1954) followed up Barcroft's animal experiments, and showed that in human beings the percentage saturation of oxygen (an index of the oxygen carrying capacity of the haemoglobin) in the umbilical vein falls from 70 to 60 per cent in the last 10 weeks of pregnancy, and between the 40th and 43rd weeks drops from 60 to 30 per cent. He shows how the so-called "unexplained" deaths rise steadily as pregnancy is prolonged. Using different methods of analysis Bancroft-Livingston and Neill (1957) were unable to confirm these findings.

The problem concerning surgical induction of labour in postmaturity is put most succinctly by Cibberd (1958) who states "we must accept that postmaturity carries an increased risk to the foetus but this is not necessarily a good reason for forcing the foetus out of the frying pan of postmaturity into the fire of surgical induction".

An examination of Table IX shows that, whereas the general hazard of foetal asphyxia in surgical induction is high, when labour was induced for postmaturity, the hazard was only 11·6 per cent. Table III however shows that where postmaturity exceeds 11 days the foetal risk of asphyxia is higher (namely 11·8 per cent, 12·1 per cent and 40·6 per cent); induction of labour at or before 16 days postmaturity, therefore, would thus seem wholly justifiable.

Foetal Position and Mode of Delivery

Table IV shows the markedly increased asphyxial risk associated with a deviation from the normal occipito-anterior position, and when operative delivery of any nature is undertaken. An analysis of the indications for forceps deliveries (Table XI) shows that the greatest incidence of anoxic damage is associated with face to pubes extraction and thus rotation before delivery is desirable.

The very high asphyxial index associated with breech deliveries stresses the increased foetal hazard, and I agree with Hall and Kohl (1956) who believe there is a tendency to over-correction in breech statistics and state "whether or not all these corrections are justified in arriving at the perinatal mortality in breech presentations is debatable". The recently reviewed standard form recommended by the Royal College of Obstetricians and Gynaecologists (1957) for the production of maternity hospital medical reports still includes prolapsed cord as a complication of breech delivery. This is undoubtedly so, but it is also a risk inherent in breech presentation as well as a complication of its delivery.

Breech extraction, with an index of 38·7, carries a much higher risk than that inherent in

TABLE XI
Indications for Forceps Deliveries

	Inertia or Delay for Reasons Other than Specified	Occipito-Posterior		Deep Transverse Arrest	Foetal Distress	Maternal Indication	Dis-proportion
		Rotated Manually	Extracted Persistent Occipito-Posterior				
Normal	79	20	6	10	10	6	7
Blue asphyxia ..	22	7	6	7	8	3	2
White asphyxia ..	6	5	4	2	6	0	1
Stillbirth	3*	0	0	0	2	1	0
Total	110	32	16	19	26	10	10
Asphyxia—per cent	25·5	37·5	62·5	47·4	53·8	30·0	30·0

* 3 stillbirths include 1 premature twin and 1 infant with gross congenital abnormalities.
The stillbirth included in "Maternal Indication" occurred in patient with eclamptic fits.

breech presentation at term and thus should not be undertaken without additional indication. Table X shows that external cephalic version before labour hardly increases the foetal risk.

In considering Caesarean section Hess (1958) states "the trend toward wider use of Caesarean section is based on the postulate that, at least in pathologic entities productive of anoxia or when the use of traumatizing forceps is anticipated, the prognosis for the infant might be improved. Parodoxically numerous reports have appeared in the literature calling attention to the high perinatal mortality in Caesarean section." Marshall and Cox (1949) state "half the foetal deaths in deliveries by Caesarean section are attributable to the risks inherent in the operation itself". The asphyxial index of 31·8 reaffirms the high rate of anoxic damage associated with abdominal delivery, and stresses the importance of the presence of an experienced resuscitator at operation.

ENGAGEMENT OF HEAD AND RUPTURE OF MEMBRANES

Table V shows that there is an increased foetal hazard when the head is not engaged before the onset of labour. If however the head be engaged, the number of weeks of engagement appears to make little difference to the foetus (6·9, 6·0 and 6·2).

Bainbridge, Nixon and Smyth (1958) found that rupture of the membranes before the onset of labour as shown by painful contractions, did not appear to be associated with any increase in the incidence of foetal distress. This survey however shows an increase in the percentage of asphyxiated babies of 43 per cent associated with rupture of the membranes before labour. Similarly Winter and Klein (1955) concluded that the longer the time interval between membrane rupture and delivery, the greater the risk of asphyxia to the baby. This would appear to be a reasonable expectation as the escape of liquor would enable the uterus to retract and impair the placental circulation.

DURATION OF LABOUR

That prolonged labour carries with it an increased risk to the foetus is an accepted fact which is substantiated by this survey (Table VI). Johnson and Clayton (1955) refer to the heavy toll of foetal life associated with a prolonged first stage of labour and attribute many of the stillbirths "to intra-uterine asphyxia arising from placental ischaemia". They assessed the placental function by its ability to transfer radio-sodium and found a consistent series of values in normal labour. In prolonged labour, however, placental action was severely reduced and in some cases was only 50 per cent of the normal mean value.

Table VI shows that a first stage of labour lasting under 24 hours is associated with no increased risk to the foetus and, furthermore, 4,476 out of 5,092 patients—i.e., 87·9 per cent—were included in this group. From 24–36 hours the risk of foetal asphyxia is increased by 41·1 per cent, whereas after 36 hours the hazard is more than doubled.

The analyses clearly show how the foetal risk of asphyxia neonatorum increases as does the length of the second stage of labour. The fact that after 2 hours in this stage the percentage rate of asphyxia is more than doubled is undoubtedly associated with the high proportion of operative deliveries that would occur.

Of greater interest perhaps is the small percentage of affected infants found when the second stage had lasted ten minutes or less. Greenhill (1947) lists the dangers of precipitate labour as follows: "Lacerations of the perineum, clitoris and cervix, post-partum haemorrhage, emphysema of the neck, haematoma of the vulva, asphyxia neonatorum, fracture of the child's skull, intracranial haemorrhage, drowning of twins in the discharges and rupture of the cord." It is with relief that one finds this paragraph concluding with the words—"however, these accidents with the exception of perineal tears, are rare".

Conger and Randall (1957) point out that precipitate delivery and precipitate labour should not be confused. The latter classification is made when the total duration of labour is under 3 hours. They find that "contrary to the popular belief, the babies behaved as well as, if not better than, those resulting from a labour designated as normal in duration". The low rate of asphyxia (5·9 per cent), shown in Table VI when the second stage of labour was 10 minutes or less in duration, indicates that this finding concerning babies resulting from a precipitate labour applies also to those resulting from a precipitate delivery.

ABO Blood Groups

At the first International Congress of Human Genetics held in Copenhagen, Roberts (1957) stated that twenty years previously, the Chairman, Sir Ronald A. Fisher, had "urged, indeed implored, those who had the facilities to look for associations between blood-groups and adult diseases". "I remember saying," he continues, "that I thought it would be more profitable to start with maternity and children's hospitals and look for selective elimination in prenatal and early life." For decades after Landsteiner had discovered the ABO system of human blood groups in 1901, little was done to seek any relationship between these antigens and disease, and in 1921 Buchanan and Higley conclude that "there is no relationship between blood groups and any disease in which sufficient data are available to justify a conclusion".

However, in more recent years, much statistical evidence has been brought forward to show that such a relationship does exist. In obstetrics after an initial impression that there might be an increased incidence of toxaemia in patients with blood group O (Pike and Dickins, 1954), no such relationship was found to exist (Dickins, Richardson, Pike and Roberts, 1956; Pearson and Pinker, 1956). Struthers (1951), investigating the fact that there were fewer group A children in AO families (father, group A; mother, group O) than in OA families (father, group O; mother, group A), found a significant excess of infants with blood group A died from bronchopneumonia.

As stated, Roberts had felt that "it would be more profitable to start with maternity hospitals" but the literature reveals no evidence of investigation into ABO groups and anoxic foetal changes. A study of Table VII shows that babies born to mothers with blood group A have a higher incidence of asphyxia neonatorum (10·5). The study is deficient in that the blood groups of the infants themselves would be important to the geneticist, and these have not been recorded. A further and more detailed study of this particular topic is being undertaken. The intriguing possibility of a hereditary influence in asphyxia has not been entertained before. This survey suggests that such a possibility exists.

Statistician's Footnote

"1. The proportions of blue to white asphyxia are reasonably homogeneous, although the contrast between the 11 to 1 obtained for group AB

and 331 to 156 for the remainder put together has a rather low probability of occurring by chance ($p = \cdot 06$). Since the AB group is small it would be unwise to attempt to make anything of this possible difference however, and it seems reasonable to go ahead by adding blues and whites together as you have done.

"2. The percentage incidences of asphyxia in the four groups were:

A	10·5
B	9·9
AB	8·2
O	9·1, overall=9·74 per cent.

"These figures tested by chi-square for goodness of fit to the overall rate of 9·74 per cent give a probability of between 0·1 and 0·2, i.e., such variation would be expected to occur about once in seven samples.

"A similar result is obtained when group A is compared only with group O, or A+B with O+AB.

"My own impression is that the maternal blood group may indeed play a part in determining the incidence of asphyxia; but in spite of the reasonable sized samples the difference does not quite reach statistical significance."

Miscellaneous Factors and Stillbirths

The high percentage of asphyxia found when the miscellaneous factors shown in Table X are studied (excluding external cephalic version) is as anticipated. "Emergency" admissions include only those cases admitted directly from the district and these form 2·7 per cent of the total admissions. The column headed "Ante-partum Haemorrhage" includes cases both of accidental and unavoidable haemorrhage. Bleeding of extra-uterine origin after the 28th week of pregnancy has not been taken into consideration. The fact that the foetal risk associated with maternal heart or lung disease is lower than average, is probably due to the small number of cases involved and although it is hardly feasible that these maternal diseases improve the foetal chances, the results indicate that the risk of anoxic damage is not increased.

In Table X, more than in any other, it may be seen that the number of stillbirths form a high percentage of the total births. This study has been concerned solely with the factors leading to anoxic damage manifest by asphyxia neonatorum, but, since an increase in either intensity or duration of these factors may result in stillbirth, it is not irrelevant briefly to consider this further. A study of all the tables shows that, in the great majority, stillbirths form only a small percentage of the total births, and thus would not appreciably alter the trends here found and recorded. The survey ratio of stillbirths is 1·5 per cent of total births, but this percentage is more than doubled in some instances and these are analyzed in Table XII.

It may thus be seen that every factor associated with a high percentage of stillbirths is also associated with an increased percentage of asphyxiated babies. The one exception is where the second stage of labour lasted less than 10 minutes, but 24 of the 27 babies (i.e., 88·9 per cent) were either premature, macerated or anencephalic, features which in themselves were responsible for the rapid delivery.

Factors in which a high percentage of asphyxia (15 per cent or more) was not associated with a corresponding increase in the incidence of stillbirths are:

(1) Persistent occipito-posterior position.

(2) Forceps extraction.

(3) Caesarean section.

(4) First stage of labour of 36 hours or more.

(5) Second stage of labour lasting 2 hours or more, and

(6) Induction of labour for pre-eclamptic toxaemia.

The fact that forceps delivery or Caesarean section may be employed to prevent stillbirth when labour is prolonged, or in persistent occipito-posterior positions, would explain the apparent discrepancy in the first five factors. In pre-eclamptic toxaemia, too, labour is induced in order to avoid stillbirth.

A consideration of stillbirths occurring in postmature foetuses shows that there were 9 stillbirths when pregnancy was prolonged by more than five days, and 2 occurred in association with surgical induction for postmaturity. A third baby was stillborn following induction

TABLE XII

Factor	No. of Stillbirths	Stillbirths as Percentage of Total Births	Remarks	Percentage of Asphyxia
Prematurity:				
–32 weeks	37	23·0		40·4
32–36 weeks				26·6
Postmaturity:				
23 days+	1	3·1	Abdominal pregnancy	40·6
Breech delivery	19	13·6	13 macerated and/or premature 3 congenital abnormalities	28·6
"Other" foetal positions	13	25·0	All anencephalic	25·0
Breech extraction	3	9·7	2 macerated twins	38·7
2nd Stage of labour:				
10 minutes or less	27	3·8	24 macerated, premature or anencephalic 1 concealed ante-partum haemorrhage 1 prolapsed cord 1 cerebral haemorrhage	5·7
Pre-eclamptic toxaemia	18	3·6	5 congenital abnormalities 7 macerated and/or premature 5 cases ante-partum haemorrhage 1 eclamptic fits	20·3
Surgical induction	26	5·2	20 for intra-uterine death or anencephalic	17·0
Emergency admission	10	7·2	4 macerated and/or premature 3 pre-eclamptic toxaemia 2 anencephalic 1 placenta praevia	21·0
Ante-partum haemorrhage ..	9	7·2	4 emergencies	27·3
Gross congenital abnormalities ..	16	30·2	13 anencephalic	30·2
Contracted pelvis	3	4·4	1 premature 1 ante-partum haemorrhage 1 prolonged labour	25·0
Twins	5	3·5	5 macerated and/or premature	25·7

One stillbirth associated with essential hypertension has not been considered.

of labour on account of breech presentation. The details of these cases are shown in tabular form (Table XIII).

Case 9 may be discounted as neither attempts to induce nor the postmaturity were factors in the stillbirth. Of the remaining eight cases, five started labour spontaneously, and deaths in four of these (numbers 1, 2, 4 and 5) were associated with anoxic conditions. In the three cases in which labour was induced (numbers 3, 6 and 8), one (case 3) was so managed because of breech presentation rather than postmaturity. Labour commenced twenty hours later and contraction ring dystocia occurred. Induction may have been a factor as it may also have been in case 6. In this latter, however, the stillbirth is more likely to have been due to postmaturity and placental insufficiency. In case 8 the cause of death was prolapsed cord which occurred with spontaneous rupture of membranes during labour and was thus not due to induction. Thus the finding previously made, that induction of labour is desirable in postmaturity, is substantiated.

It is in fact noteworthy that the trends shown by this brief additional analysis of stillbirths, in general uphold the conclusions drawn in the main substance of this survey.

Summary

A series of 5,169 consecutive deliveries conducted at Beckenham Maternity Hospital and under unchanged clinical supervision, have been studied and factors that led to the birth of 510 infants with non-fatal asphyxia have been analyzed. Asphyxia neonatorum is considered the best pointer to circumstances that may lead to the loss of foetal and neonatal life. The statistical survey, summarized in tabular form, indicates the asphyxial index of the factor under consideration. This knowledge will, it is hoped, play some part in reducing perinatal mortality.

Table XIII

	No. of Days Postmature	Time of Foetal Death	Whether Labour of Induced or Spontaneous Onset	Remarks
1	7	Before labour	Spontaneous	—
2	8	During labour	Spontaneous	—
3	6	During labour	Surgical induction—Bougie —membranes intact	Breech. Hypertonic uterus and contraction ring. Breech extraction under general anaesthetic
4	13	Before labour	Spontaneous	Emergency admission with ante-partum haemorrhage
5	14	During 2nd stage	Spontaneous	—
6	15	During 2nd stage	Surgical induction. Fore-water rupture	—
7	17	Before labour	Spontaneous	—
8	18	During 1st stage	Surgical induction membrane sweep only	Spontaneous rupture of membranes during labour and prolapsed cord
9	24	About 8 weeks before delivery	Attempts to induce 3–5 weeks before delivery failed	Laparotomy

Post-mortem examination in all cases, save number 7, revealed no abnormality other than changes attributable to asphyxia. In case 7 the cause of death was "gross congenital abnormalities" (congenital heart lesions and absent kidneys). Case 9 was grossly macerated and associated with an abdominal pregnancy.

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BLOOD PROGESTERONE LEVELS IN ABNORMAL PREGNANCIES

BY

BRUCE ETON, M.D., M.R.C.O.G.
From the Obstetrical and Gynaecological Department, United Cambridge Hospitals

AND

R. V. SHORT, Ph.D., B.V.Sc., M.Sc.(Wisconsin), M.R.C.V.S.
From the Agricultural Research Council Unit of Reproductive Physiology and Biochemistry, Department of Veterinary Clinical Studies, University of Cambridge

A RELATIVELY simple method has recently been described for the chemical determination of progesterone in peripheral blood (Short, 1958), and a series of normal values has been obtained for women from the 11th week after the last menstrual period up to the day of parturition (Short and Eton, 1959). There is reason to believe that blood progesterone levels may provide a more accurate estimate of the rate of progesterone production than urinary pregnanediol determinations (Short and Eton, 1959). The purpose of the present study has therefore been to investigate the blood progesterone levels in a number of cases of abnormal pregnancy in which it has been suggested that progesterone production might be altered.

MATERIAL AND METHODS

Sixty-nine patients were studied, and they were divided into the following groups: (1) 5 normal pregnancies, 9–11 weeks; (2) 24 women initially diagnosed as cases of threatened abortion; (3) 8 twin pregnancies; (4) 3 Rh negative women with antibodies; (5) 15 cases of pre-eclamptic toxaemia, including 3 with twin pregnancies; (6) 17 pregnant diabetics. In addition, blood was obtained from 3 normal men for "blank" plasma progesterone determinations.

Approximately 50 ml. of blood was withdrawn from the median cubital vein by allowing it to flow freely through a large-bore needle into a bottle containing heparin. Samples were obtained between 10 a.m. and 5 p.m., and were placed in a refrigerator at +5° C. immediately after collection. Subsequent procedures were exactly as described previously (Short and Eton, 1959). Of the 72 samples assayed, treatment with acetic anhydride and pyridine followed by re-chromatography was necessary in only 2 cases.

RESULTS AND DISCUSSION

(1) *Normal Pregnancies*

The findings in the previous study (Short and Eton, 1959), together with 5 additional cases from the present study, are shown in Figure 1. In comparing these normal results with those obtained in abnormal pregnancies, any values lying outside the normal range have been recorded as "low" or "high" (see Tables I–V).

During the early weeks of pregnancy, the normal progesterone levels are approaching the limits of sensitivity of the method, and little significance can be attached to values that fall below 1 μg./100 ml. plasma. When a sample of 33 ml. pooled plasma from 3 men was assayed, the progesterone concentration was found to be 0·2 μg./100 ml. plasma; another sample of

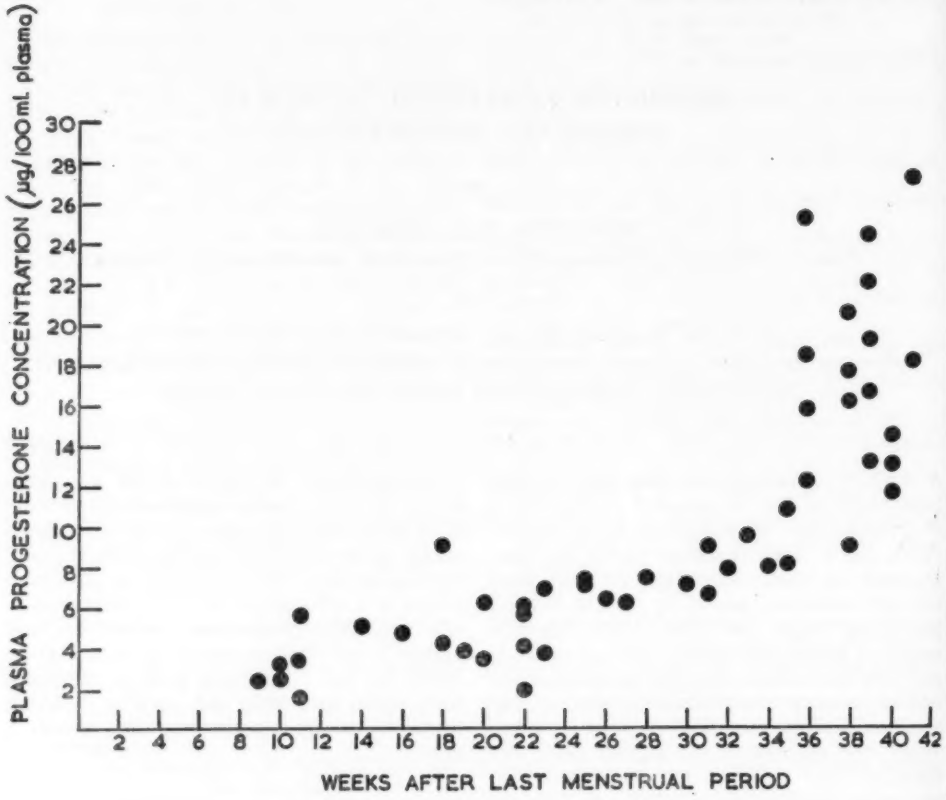

FIG. 1

Concentration of progesterone in the plasma of normal pregnant women. Results are corrected for extraction losses and expressed as μg. progesterone/100 ml. plasma.

44 ml. plasma from a man gave a "negative" result of −1·4 μg./100 ml. plasma. These plasma "blank" values are therefore well below the normal values found in early pregnancy, and they indicate that even as early as 9 weeks it is possible to detect progesterone in the peripheral blood. However, it must be emphasized that little is known of the accuracy or precision of the method at this lower end of the sensitivity scale.

(2) *Threatened Abortions*

These results are presented in Table I. Of the 24 women who were admitted to hospital with an initial diagnosis of threatened abortion, 3 were subsequently found to be non-pregnant at the time of sampling; in 2 of them, the blood progesterone level was low. Of the remaining cases, 11 women aborted within a week of the blood sample being taken, but only 3 of them had low blood progesterone levels. On the other

TABLE I

Blood Progesterone Levels in Cases of "Threatened Abortion"

Case No.	Duration of Pregnancy (weeks)	Progesterone µg./100 ml. of Plasma	Interpretation	Remarks
1 ..	22	7·4	Normal	Pregnancy continued.
1 ..	26	6·8	Normal	Inevitable abortion at time of sampling. Aborted next day.
2 ..	10	1·4	Normal	Aborted 2 days later.
3 ..	12	0·4	Low	Aborted the same day.
4 ..	11	1·4	Normal	Aborted next day.
5 ..	26?	<1·0	Low	Not pregnant.
6 ..	15	5·2	Normal	Pregnancy continued.
7 ..	10	3·1	Normal	Aborted 2 days later.
8 ..	10	0·9	Low	Abortion completed before test.
9 ..	11?	1·4	Normal	Not pregnant.
10 ..	22	5·8	Normal	Pregnancy continued.
11 ..	11	1·0	Low	Pregnancy continued.
12 ..	11	1·0	Low	Abortion complete next day.
13 ..	11	2·6	Normal	Pregnancy continued.
14 ..	11	3·1	Normal	Pregnancy continued.
15 ..	26	9·6	Normal	Premature live birth 1 week later, child died.
16 ..	11	2·4	Normal	Aborted 4 days later.
17 ..	14	3·7	Normal	Pregnancy continued.
18 ..	19	3·2	Normal	Aborted 2 days later.
19 ..	10	1·9	Normal	Pregnancy continued.
20 ..	27	6·0	Normal	Pregnancy continued.
21 ..	10	0·9	Low	Abortion almost complete.
22 ..	11	0·9	Low	Pregnancy continued.
23 ..	12	1·6	Normal	Aborted 1 week later.
24 ..	19	6·1	Normal	Aborted at 26 weeks.

hand, 11 women maintained their pregnancies for more than a week after the collection of the blood, although 2 of them had low blood progesterone levels.

It is difficult to draw any firm conclusions from these results, especially since so many of the assays were carried out during the early weeks of pregnancy when the accuracy and precision of the method are open to question. However, it is reasonable to conclude that in many cases the symptoms of threatened abortion *per se* were not associated with a low blood progesterone level, and in some women, e.g., Case 1, abortion actually occurred in spite of a perfectly normal blood progesterone level.

There is still a great deal of confusion in the literature as to the value of urinary pregnanediol determinations in cases of threatened abortion, and the subject has been well reviewed by Loraine (1958). In a recent paper, Russell, Paine, Coyle and Dewhurst (1957) state: "We have reached the firm conclusion that so far as threatened abortion is concerned single estimates of pregnanediol excretion serve little or no useful purpose." On the other hand, Shearman (1959) studied the urinary pregnanediol excretion weekly in 5 cases of first trimester abortion, the assays having been started before any clinical signs were apparent in 4 of the cases. In every instance, the pregnanediol levels were significantly below normal prior to the abortion. However, one woman who aborted at the 23rd week had a perfectly normal pregnanediol excretion up to 3 days before the abortion.

The fact that cases of abortion can occur in spite of apparently normal blood progesterone or urinary pregnanediol levels is perhaps not so surprising in view of the recent findings of Cassmer (1959). He has been able to show that experimentally-induced foetal death in women

TABLE II

Blood Progesterone Levels in Cases of Twin Pregnancy

Case No.	Duration of Pregnancy (weeks)	Progesterone µg./100 ml. of Plasma	Interpretation	Remarks
25 ..	32	19·8	High	Binovular twins, born same day.
26 ..	39	19·4	Normal	Binovular twins, born 1 week later.
27 ..	39	41·0	High	Binovular twins, born 2 weeks later.
28 ..	28	19·7	High	Binovular twins, born 8 weeks later, toxaemia.
29 ..	36	31·5	High	Uniovular twins, born 2 days later, toxaemia.
30 ..	31	13·3	High	Uniovular twins, born 6 weeks later.
31 ..	38	24·8	Normal	Binovular twins, born 1 week later.
32 ..	36	30·8	High	Uniovular twins, labour induced 3 weeks later, toxaemia.

TABLE III

Blood Progesterone Levels in Women with Rhesus Antibodies

Case No.	Duration of Pregnancy (weeks)	Titre of Antibodies	Progesterone µg./100 ml. of Plasma	Interpretation	Remarks
33 ..	39	1:16 throughout pregnancy	16·1	Normal	Labour induced, child lived after exchange transfusion, mildly affected.
34 ..	37	1:4→1:32	23·3	Normal	In labour, child lived after 2 exchange transfusions, fairly severely affected.
35 ..	39	1:8 throughout pregnancy	16·4	Normal	Labour induced, child lived after exchange transfusion, mildly affected.

TABLE IV

Blood Progesterone Levels in Cases of Pre-eclamptic Toxaemia

Case No.	Duration of Pregnancy (weeks)	Degree of Toxaemia	Progesterone µg./100 ml. of Plasma	Interpretation	Remarks
28 ..	28	Mild	19·7	High	Binovular twins born 8 weeks later.
29 ..	36	Mild	31·5	High	Uniovular twins born 2 days later.
32 ..	36	Mild	30·8	High	Uniovular twins, labour induced 3 weeks later.
36 ..	37	Mild	10·0	Normal	Normal delivery 2 weeks later.
37 ..	29	Severe	8·8	Normal	Intra-uterine death 3 weeks later.
38 ..	35	Moderate	10·3	Normal	Ante-partum haemorrhage, live birth next day.
39 ..	39	Moderate	16·6	Normal	Labour induced, live birth next day.
40 ..	38	Moderate	16·4	Normal	Labour induced, live birth next day.
41 ..	40	Mild	18·6	Normal	Caesarean section 1 week later.
42 ..	35	Mild	9·5	Normal	Caesarean section 3 weeks later.
43 ..	39	Mild	22·6	Normal	Labour induced, live birth next day.
44 ..	38	Severe	14·2	Normal	Labour induced 2 days later, stillbirth (spina bifida).
45 ..	36	Mild	20·0	Normal	Spontaneous delivery 3 weeks later.
46 ..	41	Mild	7·9	Low	Spontaneous delivery next day.
47 ..	40	Mild	12·0	Normal	Labour induced, live birth next day.

has very little effect on urinary pregnanediol excretion, although it is a major factor in inducing abortions. Furthermore, progesterone production does not appear to be diminished even during normal parturition (Aitken, Preedy, Eton and Short, 1958).

(3) *Twin Pregnancies*

Blood progesterone levels were estimated in 8 women with twin pregnancies (see Table II); this series includes 3 results that have been published previously (Short and Eton, 1959). In 6 out of the 8 cases, including 3 women with toxaemia, the blood progesterone levels were high, and this was irrespective of whether the twins were uniovular or binovular. These findings are probably explained by the increased placental size, and hence increased progesterone production, in twin pregnancies. It is therefore surprising that Shearman (1959) failed to find any significant increase in urinary pregnanediol excretion in cases of twin pregnancy.

(4) *Rh Negative Women with Antibodies*

These results are presented in Table III, and they are all within the normal range. Russell *et al.* (1957) similarly noted normal urinary pregnanediol excretion values in cases in which the child was born alive.

(5) *Pre-eclamptic Toxaemia*

Blood progesterone determinations were carried out in 15 patients suffering from pre-eclamptic toxaemia. For the purposes of this investigation, patients were selected who had albuminuria and hypertension (blood pressure at least 140 mm. Hg systolic or 90 mm. Hg diastolic) on several occasions. Toxaemia was classed as mild in 10, moderate in 3 and severe in 2 patients. Three patients (Nos. 28, 29, 32) had a twin pregnancy. Progesterone levels were normal for the corresponding stage of pregnancy in all patients except No. 46, in which it was low, and in the 3 twin pregnancies, where it was high, as might have been expected.

These results are therefore in disagreement with many of the urinary pregnanediol findings of other workers, who have recorded low values (Russell *et al.*, 1957; review by Loraine, 1958; Shearman, 1959). Furthermore, they do not support the theories of Dalton (1957), who has suggested that the symptoms of impending toxaemia are due to a progesterone deficiency.

The explanation for this discrepancy between the findings in blood and urine could be an impaired renal clearance of pregnanediol in cases of toxaemia.

(6) *Pregnant Diabetics*

The blood progesterone levels in 17 pregnant diabetic women are shown in Table V, and it will be seen that in 7 cases the values are above the normal range. Three of these 7 women subsequently lost their babies, whereas only 1 of the 10 women with normal progesterone levels lost her baby; in her case, 10 weeks had elapsed between the collection of the blood and the death of the foetus.

It is difficult to understand the reasons for the high blood progesterone levels encountered in some pregnant diabetics. From Figure 1 it can be seen that in normal pregnancies the blood level rises sharply between the 36th week and term; however, the reason for this is obscure. It may be that the high levels in the pregnant diabetics are an early manifestation of this same rise.

White and her collaborators (White and Hunt, 1943; White, 1947, 1952; Nelson, Gillespie and White, 1953) put forward the theory, based on the results of urinary pregnanediol determinations, that a progesterone deficiency may occur in pregnant diabetics; furthermore, they indicated that progesterone therapy in such cases had a marked effect in improving the foetal prognosis. The Medical Research Council (1955) therefore carried out a carefully controlled clinical trial which was designed to assess the effect of oral stilboestrol and ethisterone therapy on the foetal survival rate in pregnant diabetics. However, it was found that the frequency of stillbirths and neonatal deaths in treated and control groups was almost identical. More recently, Russell *et al.* (1957) failed to find any abnormalities in urinary pregnanediol excretion in a group of 23 pregnant diabetics, regardless of the outcome of the pregnancy. From their results, together

TABLE V

Blood Progesterone Levels in Pregnancies Complicated by Diabetes

Case No.	Duration of Pregnancy (weeks)	Progesterone µg./100 ml. of Plasma	Interpretation	Remarks
48 ..	33	17·0	High	Stillbirth at 35 weeks.
49 ..	26	4·1	Normal	Stillbirth at 36 weeks.
50 ..	37	10·6	Normal	Induction at 38 weeks, live child.
51 ..	31	21·5	High	Caesarean section at 33 weeks, neonatal death.
52 ..	35	15·4	High	Induction at 37 weeks, live child.
53 ..	34	10·3	Normal	Caesarean section at 37 weeks, live child.
54 ..	34	8·2	Normal	Caesarean section at 37 weeks, live child.
55 ..	35	18·0	High	Induction at 37 weeks, live child.
56 ..	35	13·4	Normal	Caesarean section at 37 weeks, live child.
57 ..	35	9·8	Normal	Caesarean section at 37 weeks, live child.
58 ..	35	13·0	Normal	Induction at 37 weeks, live child.
59 ..	35	15·1	Normal	Induction at 36 weeks, live child.
60 ..	35	15·8	High	Induction at 37 weeks, live child.
61 ..	34	6·7	Normal	Caesarean section at 38 weeks, live child.
62 ..	34	7·1	Normal	Caesarean section at 36 weeks, live child.
63 ..	35	28·2	High	Caesarean section at 37 weeks, live child.
64 ..	34	20·4	High	Caesarean section at 36 weeks, neonatal death.

with those presented in Table V, there is nothing to suggest that a progesterone deficiency occurs in pregnant women suffering from diabetes.

SUMMARY

Blood progesterone determinations were carried out in the following groups of patients:

(1) Twenty-four women initially diagnosed as cases of threatened abortion.

(2) Eight women with twin pregnancies.

(3) Three Rh negative women with antibodies.

(4) Fifteen women with pre-eclamptic toxaemia.

(5) Seventeen pregnant diabetics.

In the threatened abortion group, no definite conclusions could be reached as to the value of blood progesterone assays, since the levels found in many cases were approaching the limits of sensitivity of the method. However, it became apparent that some women aborted in spite of perfectly normal blood progesterone levels.

Six of the 8 women with twins, including 3 with symptoms of pre-eclamptic toxaemia, showed high blood progesterone levels. It was thought that this might be explained by the increase in the size of the placenta.

The 3 Rh negative women with antibodies all had normal blood progesterone levels.

Of the 15 women with pre-eclamptic toxaemia, only 1 had a low blood progesterone level.

Seven of the 17 pregnant diabetics had high blood progesterone levels, and 3 of them subsequently lost their babies. On the other hand, only 1 of the 10 women with normal progesterone levels lost her baby.

These findings therefore differ in a number of respects from the results obtained by urinary pregnanediol determinations in the same conditions.

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RUPTURE OF VARICOSE VEINS OF THE UTERUS ASSOCIATED WITH PREGNANCY

BY

A. E. MARROW, M.R.C.O.G.
Obstetrician and Gynaecologist
Nottingham Hospital for Women

DURING pregnancy interference with venous return by the enlarging uterus and hormone relaxation of smooth muscle predispose to varicose veins of the lower extremities and genital tract.

It is therefore perhaps rather surprising that rupture of varicose veins of the uterus and broad ligament should be, apparently, a rare complication of pregnancy and the puerperium.

When rupture does occur the bleeding may be either intra-peritoneal, retro-peritoneal or mixed in type.

When the vein is situated on the uterus the bleeding is always intra-peritoneal as there is no loose-tissue space in which the blood can collect. When the vessel is in the broad ligament, the bleeding may be either retro-peritoneal or, if extensive enough to cause rupture of the peritoneum, mixed in type.

In the first case the picture should, of course, be principally that of haemo-peritoneum, and the presenting features will be pain, shock and collapse. In the second case the picture tends to be less definite and the signs and symptoms may be confusing. In the majority of cases described in the literature a correct pre-operative diagnosis was not made.

In 1950 Hodgkinson and Christensen collected 72 cases from the literature and described 3 more.

They noted that only 60 per cent of the cases were associated with labour, and that the mortality rate was 49·3 per cent.

In some cases there was a definite history of trauma immediately prior to the onset of symptoms; for example that reported by Harding and Concannon (1943) when coitus had taken place half an hour previously.

They described 3 further cases, 2 of massive intra-peritoneal haemorrhage treated conservatively and diagnosed only at post-mortem. The third case showed a large abdominal mass and at laparotomy a haematoma arising in the right broad ligament and extending upwards almost to the kidney region was excised (see Table I).

In 1952 Hodgkinson described a further case in which, by the light of his previous experience, he was able to make a diagnosis of rupture of a left utero-ovarian varix. He performed a Caesarean section and sutured the varix and the patient survived.

In 1955 Jurishica and Gutglass reported 2 cases. In one, occurring three hours post-partum, there was a massive mixed retro- and intra-peritoneal haemorrhage and the patient was in a state of severe shock and collapse. Following a diagnosis of internal bleeding, laparotomy was performed with total hysterectomy and bilateral salpingo-oöphorectomy. In the second case, which occurred eighteen hours post-partum, the bleeding was much less severe, though mixed in type, and the pre-operative diagnosis was mechanical obstruction.

Jurishica and Gutglass concluded that periodic contractions of the uterus may control the bleeding in part, and then the symptoms produced are those due to the mass of the haematoma rather than the blood loss; and are likely to be pain, tenderness, and paralytic ileus. They suggest that such cases would recover if left, since the bleeding would stop in time without any operative interference.

TABLE I

Authority	Date	Age of Patient	Previous Pregnancies	Time of Incident	Principal Signs and Symptoms	Pre-operative Diagnosis	Treatment	Type of Bleeding	Result
Hodgkinson and Christensen (1950)	1930	24	0	12 hours post-partum	Shock	—	Conservative	Mixed	Died after 24 hours
Hodgkinson and Christensen (1950)	1944	20	0	14 days post-partum	Pain and abdominal mass	Abdominal mass	Excision of haematoma (8×8×5 cm.)	Retro-peritoneal	Lived
Hodgkinson and Christensen (1950)	1947	35	4	Immediate post-partum	Shock	—	Conservative	Mixed	Died after 2 hours
Hodgkinson (1952)	1950	30	1	36/52	Pain and mass	Rupture of left utero-ovarian varix	Caesarean section and suture	Intra-peritoneal	Lived
Jurishica and Gutglass (1955)	1948	33	0	18 hours post-partum	Pain, bowel distension	Obstruction due to adhesions from previous appendicectomy	Caecostomy	Retro-peritoneal	Lived
Jurishica and Gutglass (1955)	1951	37	1	3 hours post-partum	Profound shock	Internal haemorrhage	Total hysterectomy	Intra-peritoneal	Lived
Finch (1956)	1956	32	0	28/52	Pain	Accidental A.P.H.	Caesarean section and ligation of varix	Intra-peritoneal	Lived
Maier (1958)	1950	26	1	34/52	Pain	Accidental A.P.H.	Caesarean section and ligation of varix	Intra-peritoneal	Lived
Maier (1958)	1955	43	0	35/52	Pain	Accidental A.P.H.	Caesarean section and ligation of varix	Intra-peritoneal	Lived
Marrow No. I	1959	40	3	36/52	Pain and tenderness	Acute appendicitis	Caesarean section and ligation of varix	Intra-peritoneal	Lived
Marrow No. II	1958	22	0	36/52	Pain and then shock	Haemo-peritoneum	Caesarean section and ligation of varix	Intra-peritoneal	Lived

In 1956 Vernon Finch reviewed the literature and reported another case. He stressed again the rarity of the condition and the fact that it was so infrequently described in medical textbooks.

He found that 50 per cent of cases occurred in primiparae; that the average age of incidence was 28·6 years and that 60 per cent occurred during labour. In 78 per cent of cases the bleeding was from the broad ligament, in 19 per cent from the posterior surface of the uterus and in 3 per cent from the anterior surface of the uterus.

He found the mortality to be 46 per cent, but 76 per cent when the patient was in labour, as the presence of labour pains made the diagnosis more difficult.

He stressed the importance of shock and peritoneal irritation as presenting signs and the fact that a decision as to the management of the case could usually be made even in the absence of the correct diagnosis.

This is also the point that Maier (1958) stressed when he reported 2 further cases, one intra- and one retro-peritoneal in type, both with a pre-operative diagnosis of placental separation and neither showing profound shock. He states "one can only postulate that the large gravid uterus may have exerted a tamponading effect so that the blood loss was only intermittent".

In the 2 cases reported below this fact also emerges. There was no correct pre-operative diagnosis, but it was obvious that laparotomy was essential.

CASE HISTORIES

Case 1

The patient (a doctor's wife) was aged 40 years and this was her fourth pregnancy. She had had normal spontaneous deliveries at full term in 1949, 1950 and 1955.

There was no relevant past history.

Her last menstrual period had begun on the 1st January, 1959 and the pregnancy had progressed normally until the 26th September, 1959.

At 11 a.m. on that day, while being driven to the local town by her husband, there was a sudden onset of lower abdominal pain on the right side and supra-pubically. She had no other symptoms but was immediately taken to Grantham Hospital. There her general condition was found to be satisfactory, but transfer to the Women's Hospital, Nottingham, was arranged by telephone.

On admission there her general condition was good; pulse 82, temperature 96·8, blood pressure 130/70, urine normal. Her blood was known to be Group A Rhesus negative.

There was marked extra-uterine tenderness on the right side of the abdomen, with a point of maximum tenderness two inches below the umbilicus and just to the right of the uterine border.

The height of the fundus corresponded to a pregnancy of 36 weeks; the presentation was a vertex.

The foetal head was engaged and the foetal heart heard. On vaginal examination the cervix was found to be taken up and the os admitted one finger, but the patient was definitely not in labour.

In view of the right-sided pain and tenderness a diagnosis of acute appendicitis was made and a general surgeon consulted. Immediate laparotomy was decided on.

The patient's general condition remained entirely satisfactory and there was nothing at any time to suggest haemo-peritoneum.

At 4.30 p.m. laparotomy was performed through a McBurney's incision, and a large quantity of fresh blood was found in the abdomen. The wound was closed and the abdomen re-opened through a left paramedian incision, and a lower segment Caesarean section performed. A live healthy male child weighing 6 pounds 7 ounces was delivered.

There were several varicosities on the anterior surface of the uterus but no bleeding from any of these.

On the posterior aspect of the uterus just below the cornu was a leash of bleeding varicose veins. The broad ligament veins on both sides were grossly distended. Considerable difficulty was experienced in controlling the bleeding until finally a figure of eight suture round one of the larger vessels proved successful.

It was felt that hysterectomy carried too great a risk of considerable haemorrhage from the massive veins.

The patient was given a transfusion of two pints of Dextrose and two pints of blood. Since she was Rhesus negative there was some delay in obtaining blood, but her condition remained satisfactory throughout.

Two days after operation her Hb was 9·6 g. per cent and three days later 10 g. per cent. Her post-operative progress was satisfactory, except for a cough and some breaking down of the abdominal wound on the sixth day.

The most salient feature of this case was the absence of shock and shoulder pain, and of gross anaemia in spite of very considerable bleeding. This was probably due in part to the absence of delay: firstly because the catastrophe occurred in the presence of a doctor; secondly, because in late pregnancy, when there is abdominal pain and tenderness, if there is no clear-cut diagnosis, I make it an absolute rule never to refrain from laparotomy without a second opinion.

Case 2

The patient, a primigravida, was aged 22 years.

She had had pleurisy 1 year previously, and after this had attended a chest clinic for some months.

Her last menstrual period had commenced on the 25th March, 1958 and apart from a possible pyelitis at 18 weeks had progressed normally.

At 3 p.m. on the 2nd December, 1958, the patient was admitted with a history of sudden onset of abdominal pain three hours previously. The pain was continuous but became worse at times.

On admission her general condition was fair, pulse 100, temperature 98, blood pressure 120/75, urine normal. Her blood was known to be Group A Rhesus positive.

The abdomen was tense and very tender, and a diagnosis of concealed accidental haemorrhage or pyelitis was made.

By 8.15 p.m. the patient had developed shoulder pain, dullness in the left flank and increasing pallor and her pulse had risen to 110. A diagnosis of haemo-peritoneum was made. Rupture of the spleen was considered to be the most likely cause.

At 10.45 p.m., after consultation with a general surgeon, laparotomy was performed. A considerable amount of free blood was found in the peritoneal cavity and after Caesarean section a tear in the left broad ligament and ruptured veins were detected and sutured.

The child, a female, weighing 5 pounds 11 ounces, was alive and healthy.

The patient made an uneventful recovery. During operation she was given a transfusion of two pints of blood.

This case illustrates once again that, even in the absence of a correct diagnosis, there is no doubt of the correct treatment; laparotomy with Caesarean section followed by control of the haemorrhage.

Table I shows the 11 cases reported since the 72 collected by Hodgkinson and Christensen in 1950.

It shows a reduction in the maternal mortality from 49·3 per cent in the original group to 18·2 per cent; and illustrates well the necessity for early laparotomy even in the absence of a definite diagnosis, since the only 2 deaths are

those which had conservative treatment, and where the diagnosis was made post-mortem.

It illustrates also the difficulty in making a correct pre-operative diagnosis. The only case where this was done was the last case reported by Hodgkinson (1952), who already had considerable experience of the condition from a study of the cases he had previously reported.

One is left wondering how many fatal cases of obstetric shock in the past may have been due to rupture of pelvic varicosities, and how many cases of pregnancy and puerperal ileus may be due to the retro-peritoneal type of haemorrhage.

In spite of these possibilities of missed diagnosis in the past, it is a rare condition, but one which should be borne in mind when considering the differential diagnosis in the acute abdominal catastrophe in pregnancy and the puerperium.

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THE MANAGEMENT OF RENAL FAILURE FOLLOWING SEPTIC ABORTION

BY

F. A. L. DA CUNHA, M.B., B.Clin., M.R.C.O.G.
Consultant Obstetrician and Gynaecologist

T. H. LEAN, M.B., B.S.
Registrar in Obstetrics and Gynaecology, Oldham

C. R. BLAGG, M.B., M.R.C.P.
Research Fellow, Department of Medicine

AND

F. M. PARSONS, B.Sc., M.B., Ch.B.
Assistant Director, Metabolic Disturbances in Surgery M.R.C. Unit
From the Oldham General Hospital and The General Infirmary at Leeds

Clostridium welchii infection following septic abortion and complicated by renal failure is well recognized and has been reviewed by several writers (Douglas *et al.*, 1953; Godsick *et al.*, 1954; De Alvarez and Wolter, 1958).

Though positive bacteriological culture was not obtained during the acute phase of the illness in this case, the clinical features closely resembled those of proven *Cl. welchii* infection in other reported cases, and the rapid onset of the toxaemia, the severity of the illness, and the successful conservative management including the use of the artificial kidney are thought worthy of record.

CASE REPORT

History

Mrs. P.H., age 21 years, who had had 2 previous full-term normal confinements, was admitted to Oldham Hospital at 5.30 a.m. on the 27th November, 1958, with a history of lower abdominal pain and vaginal bleeding of about 6-hours duration. Her last menstrual period was in mid-June, 1958. She maintained that she did not know that she was pregnant and strongly denied any suggestion of criminal interference.

Condition on Admission

Her general condition was good. The temperature was 99° F., the pulse rate was 80 per minute and the blood pressure was 120/80. The size of the uterus was that of a 24-weeks pregnancy; the uterus was tense and moderate contractions were occurring every 3 to 5 minutes. Foetal parts were palpable, but foetal heart sounds could not be heard. There was acute tenderness over the left loin and lower abdomen. There was a small amount of old blood clot visible at the vulva.

Progress

At 1.20 p.m. on the same day, abortion occurred of a fresh foetus weighing 6 ounces accompanied by the loss of 14 ounces of old blood. The placenta was retained and this was removed by sponge forceps under gas and oxygen anaesthesia one hour and forty minutes later. During the same evening and night, she became restless and vomited several times. The next day the restlessness became more marked and she complained of severe abdominal pain. The temperature was 98° F., the blood pressure was 115/80, and the pulse rate had risen to 132 per minute. The skin was pale and dry, the tongue furred, the lips and ears were slightly cyanotic and there was an icteric tinge of the sclerae. The abdomen was distended and tenderness and rigidity were present in both lower quadrants. At this stage a provisional diagnosis of peritonitis was made.

The laboratory findings were: Hb. 73 per cent, Group B Rh positive, R.B.C. 3·87 million/c.mm., W.B.C. 16,400/c.mm. (82 per cent neutrophils), bilirubin 0·95 mg. per cent and the blood urea 42 mg. per cent. A high vaginal swab was taken and reported later to grow *Staphylococcus albus* but no anaerobes were isolated.

Treatment

She was given soluble penicillin, ½-million units every 6 hours and oxytetracycline 250 mg. every 6 hours in a 5 per cent dextrose-saline intravenous drip. During the second day her condition deteriorated. The temperature rose to 102° F. and the pulse rate to 148 per minute. Patchy areas of purple discolouration of the skin developed in both groins and over the right loin. The abdominal distension had increased and the tenderness was now generalized. Bowel sounds were absent. She was very drowsy and confused. The haemoglobin had fallen to 45 per cent and transfusion with concentrated red blood cells was commenced, further transfusions being given each day. The urine output was only 360 ml. and the blood urea had risen to 176 mg. per cent. One litre of 10 per cent solution of dextrose plus any visible loss of fluid was given parenterally by means of a polythene catheter passed into her left subclavian vein.

At this stage the development of increasing toxaemia, associated with the skin discolouration and with the rapidly falling haemoglobin, suggested the possibility of gas gangrene infection despite the negative anaerobic culture of a high vaginal swab. A total of one million units of polyvalent anti-gas gangrene serum was given in divided intravenous doses over the next four days. On further questioning the patient admitted that abortion had been induced with soap and water injection the day before admission. The temperature and pulse rate had fallen to nearly normal values by the 7th day but the haemoglobin was only 56 per cent, although 8 pints of concentrated red blood cells had been transfused. The urine output continued to decrease whilst the blood urea rose, being 560 mg. per cent on the 6th day and 760 mg. per cent on the 7th day. Although the infection was subsiding it seemed unlikely that she would recover from the uraemia. She was transferred to the Artificial Kidney Unit in the General Infirmary at Leeds on the evening of the 7th day.

On arrival in Leeds the patient was in semi-coma. There was slight oedema of the sacrum and ankles. The blood pressure was 130/70. Paralytic ileus was still present, and there was tenderness over the lower abdomen. The uterus had not involuted, the fundus reaching the umbilicus.

The blood chemistry (Fig. 1) revealed a severe degree of uraemia and an emergency haemodialysis was started at 00.15 hours. During the procedure 75,000 units of mixed gas-gangrene anti-toxin was given after a test dose produced no reaction. Two and a half hours later she became disorientated and developed circumoral pallor, flushing of the face and profuse sweating. There was no urticarial eruption or bronchospasm. This was thought to be due to the anti-toxin and 50 mg. of promethazine hydrochloride was given with some relief. Four hours fifty minutes after the start of the dialysis a severe convulsion occurred which was controlled by 0·05 g. of thiopentone. Twenty minutes later there was a further convulsion and the dialysis was stopped. A third fit occurred twenty minutes later, which was again controlled by thiopentone. One pint of concentrated red blood cells was given after the conclusion of the dialysis.

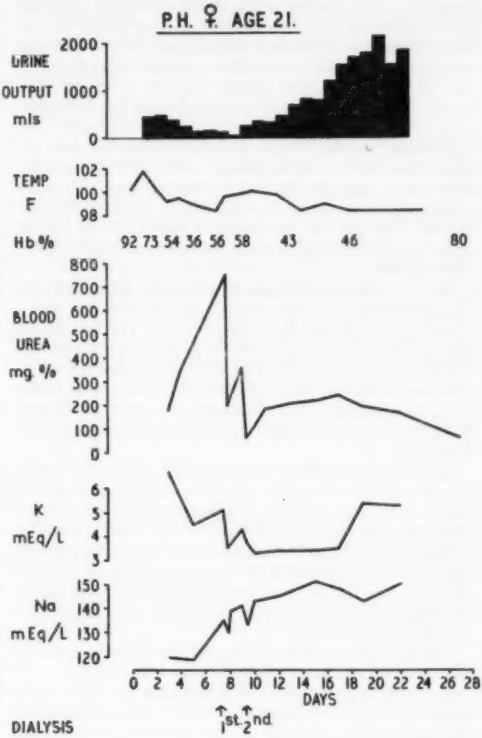

FIG. 1

Three hours after the third convulsion she regained consciousness but fluid had to be given parenterally. One million units of penicillin were given 4-hourly, and 100 mg. of oxytetracycline was given 6-hourly for the next 10 days.

Prior to the dialysis the average daily rise of the blood urea had been 144 mg. per cent. Norethandrolone, 50 mg. per day, was commenced on the 8th day to reduce the protein catabolic rate. As the blood urea rose 155 mg. per cent during the next 24 hours it seemed unlikely that norethandrolone would be effective without a second dialysis which was performed on the 9th day. No untoward episode occurred during this dialysis except for a slight epistaxis which cleared spontaneously. As the anaemia was still severe a further two pints of concentrated red blood cells was given at the conclusion of the dialysis.

The next day there was a profound change in the clinical condition. The patient was fully conscious and rational. The paralytic ileus was no longer present and she was able to take 400 ml. of 25 per cent glucose with

vitamins orally. Examination of the abdomen revealed that tenderness was less marked and confined to the lower abdomen. Following this second dialysis the rate of protein catabolism was reduced significantly, the daily rise of the blood urea being very low (Fig. 1). The anuric dietary regime was continued until the 16th day, even though the patient complained of hunger. The tenderness in the lower abdomen subsided but no involution of the uterus had occurred. The cervix was fixed by a mass in the left parametrium. Short wave diathermy to the pelvis was started on the 15th day. As on the 13th day the haemoglobin had fallen to 43 per cent two pints of concentrated red blood cells were given the next day.

On the 16th day 500 ml. of milk was given and this was increased to 1 litre per day on the next day and a full diet was allowed from the 18th day. The first fall in the B.U.N. occurred when the daily urine output reached 800 ml. on the 18th day (Fig. 1). Her general condition improved steadily. The uterus, however, remained bulky and no involution had occurred. She was transferred back to Oldham Hospital for further treatment on the 27th day.

On arrival in Oldham her general condition was good. The blood urea was 62 mg. per cent and 5 days later had fallen to 42 mg. per cent. The haemoglobin was 80 per cent and rose over the same period to 95 per cent. The Fishberg renal function test showed a maximum specific gravity of 1,010 and the urea concentration of 2 grams per cent. Despite this evidence of poor renal function an intravenous pyelogram was satisfactory and revealed a normal renal tract.

On the 46th day irregular vaginal bleeding commenced and became moderately heavy. This was thought to be due to retained products of conception and the uterus was, therefore, evacuated of a considerable quantity of placental debris. Culture of the specimen gave a pure growth of *Cl. welchii*. On the 61st day the blood urea had fallen to 32 mg. per cent and she was discharged on the following day.

Discussion

Certain features pointed to the likelihood of *Cl. welchii* infection, in the absence of clear proof on culture.

The onset of fever, lower abdominal pain and vomiting soon after interference has taken place, as also the disproportionately high pulse rate in relation to the temperature, have all been noted by other writers (Douglas *et al.*, 1953) and were present here. The associated septicaemia and toxaemia caused haemolysis giving rise to jaundice and vascular collapse with cyanosis (Ramsey, 1949; Godsick *et al.*, 1954; De Alvarez and Wolter, 1958); this was evident in the cyanosis of the lips and ears, the purple discolouration of the skin over the groins and in the right loin, and in the icteric tinge of the sclerae.

That rapid haemolysis was proceeding was evident from the rate of fall in haemoglobin values from 73 per cent on the day after admission to 45 per cent on the third day and to 36 per cent on the fourth day (Fig. 1) despite transfusions of packed cells. Over-transfusion with red cells when haemolysis is occurring may result in further elevation of the blood urea in acute renal failure and should be avoided (De Alvarez and Wolter, 1958). Despite the giving of eight pints of concentrated red cells, the haemoglobin was only 56 per cent on the seventh day.

Still more striking was the acute rise in the blood urea at an early stage of the illness, from 42 mg. per cent on the day after admission to 176 mg. per cent on the third day. This has been noted by other authors (De Alvarez and Wolter, 1958).

It is significant that this rapid onset of uraemia occurred despite the prompt institution of the dietary regime at the commencement of the oliguric phase. The blood urea level continued to rise 140 mg. per cent per day after the third day even though the *Cl. welchii* infection was being brought under control by combined penicillin, oxytetracycline and polyvalent anti-gas gangrene serum.

On the seventh day, as it was clear that death from uraemia was imminent, she was transferred to the Artificial Kidney Unit at Leeds.

Previous experience with patients in advanced uraemia with a high protein catabolic rate, made it imperative to perform a haemodialysis on admission (Parsons and McCracken, 1959). The severity of the uraemic state was further emphasized by the occurrence of convulsions during the dialysis which necessitated terminating the procedure before adequate biochemical correction had been achieved. A second dialysis was, therefore, necessary 36 hours later and at the conclusion the blood urea had fallen to 61 mg. per cent. After the first dialysis, norethandrolone, 25 mg. b.d., was given and, following the second dialysis, a profound decrease in the rate of protein catabolism occurred. The reduction was probably in part

due to the timely dialysis and in part due to the known action of norethandrolone in acute renal failure from obstetric causes (McCracken and Parsons, 1958). At the same time a profound improvement in the clinical condition occurred. In particular, cerebration returned to normal, the tenderness in the lower abdomen subsided rapidly and oral feeding was commenced as normal intestinal peristalsis returned. Thereafter, renal function gradually improved and the patient continued to make an uninterrupted recovery, except that retained products had to be removed on the 46th day.

Postscript

Four months after discharge from hospital, the patient reported with seven weeks amenorrhoea. Examination revealed a retroverted, enlarged and softened uterus, and the Hogben test was positive.

This pregnancy progressed normally until the 37th week. At no time did she develop albuminuria or hypertension, and at the 34th week of pregnancy the blood urea was 14 mg. per cent, the urea clearance was 135 per cent of average normal function, and the Fishberg Specific Gravity Test was normal. At the 37th week she was admitted to hospital for treatment of a mild urinary infection, and was discharged 12 days later.

The estimated date of confinement was 25th January, 1960, and she was admitted in labour 6 days later. The head was engaged in the pelvis, and after regular contractions had been observed for two hours—the foetal heart being present—the contractions stopped and the foetal heart disappeared.

Although her general condition remained good (blood pressure 110/90), generalized abdominal tenderness and a rising pulse rate suggested rupture of the uterus.

Laparotomy confirmed a large vertical rent in the left lateral wall of the uterus, extending to the fundus. The trunk of the child and the placenta were free in the peritoneal cavity. The child was extracted and a subtotal hysterectomy carried out.

She was discharged home 14 days after operation, during which period the urine remained albumin-free, the blood pressure normal, and five days after discharge from hospital a urea concentration test was carried out with the following results: 1st specimen, 32 c.cm., 4·6 per cent urea; 2nd specimen, 42 c.cm., 4·7 per cent urea; 3rd specimen, 33 c.cm., 4·7 per cent urea.

Acknowledgments

Our thanks are due to Professor W. I. C. Morris, Manchester, Dr. O. Janus, Oldham, and Mr. J. B. Farquhar, Leeds, for invaluable advice during the acute phase of the illness.

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ECLAMPSIA COMPLICATING HYDATIDIFORM MOLE

BY

JOSEPH ALVEY, M.B., M.A.O., M.R.C.O.G.
Assistant Master
National Maternity Hospital, Dublin

ECLAMPSIA complicating hydatidiform mole is a rarity. Theobald (1955) remarked that eclamptic convulsions had never been seen as a complication of hydatidiform mole "by any living English author". This statement is still true, apparently. Chesley, Cosgrove and Preece (1946), however, recorded a case in America and these authors reviewed the literature, discovering 35 other cases since 1866.

In view of the rarity of the condition, it seems of interest to report the following case. Other arresting features of the case were prolonged coma, treated by tracheostomy, and hyperpyrexia, treated by artificial cooling.

CASE REPORT

Mrs. M.K. (Reg. No. 61,672) was admitted unconscious to the National Maternity Hospital, Dublin, on 9th February, 1958. She had been sent in as an emergency from a distance of 50 miles. From her husband, her family doctor, and subsequently from the patient herself, the following history was obtained.

The patient was aged 43 years and had been married for 1 year. There was no history of serious medical disease or surgical operations. Specifically, there was no history of epilepsy in the patient or her family. Menstruation had been regular until 3 or 4 months before admission. Noticeable abdominal enlargement had been present for 1 month and marked swelling of the legs for 1 week.

On the day of admission, the patient's husband had been awakened at 1 a.m. to find his wife in the throes of a convulsion. While awaiting the arrival of the family doctor and of the ambulance, the patient had 20 fits. A further 2 fits occurred while she was being transported to hospital. She was unconscious from the time of the first fit.

On admission she was found to be poorly nourished and oedematous, with a slight icteric tinge. She was irritable, although quite unconscious. The body temperature was 101° F. (38·3° C.), the pulse rate 120, and the respiratory rate 30 per minute. The blood pressure was 150/110. There was marked oedema of the legs and feet and some oedema of the vulva and hands. Catheterization produced 3½ ounces (99·4 ml.) of slightly blood-stained urine. This showed +3 proteinuria (approximately 500 mg. per 100 ml.), a fair number of leucocytes, numerous red blood cells and very numerous granular casts.

The breasts were active. No abnormality was detected in the heart and the lung-fields were normal.

On abdominal examination there was an irregular mass arising from the pelvis to the size of a 28-weeks pregnancy. The consistency of the mass, however, was that of fibromyomata. No foetal heart could be heard. Vaginal examination was difficult, but the pelvis seemed to be occupied by a large fibromyomatous mass. The cervix was small, soft and wedged against the symphysis pubis.

Examination of the central nervous system revealed no gross abnormality. The reflexes were generally depressed, the pupils were equal and reacted to light. There was no neck rigidity and the plantar responses were flexor. The patient was incontinent of faeces and urine.

Because of the pyrexia, the patient was transferred to the isolation ward. Five hours after admission she had a fit lasting 2 minutes and 7 hours later another fit lasting 1 minute. The body temperature rose to 104° F. (40° C.). Antibiotic therapy was started.

Laboratory Investigations

Blood group O Rhesus (D) positive; haemoglobin 11·3 g. (79 per cent); Wassermann reaction negative; blood urea 137 mg. per 100 ml.; blood sugar 136 mg. per 100 ml.; total plasma protein 4·5 g. per 100 ml.; plasma albumin 2·0 g. per 100 ml.; plasma globulin 2·5 g. per 100 ml.; serum bilirubin 1 mg. per 100 ml.; serum alkaline phosphatase less than 8 units per 100 ml. (King-Armstrong); thymol turbidity 1 unit; Widal reaction negative.

Cerebrospinal fluid was clear and under normal pressure. The Queckenstedt test was positive. The fluid contained polymorphonuclear leucocytes 85 per c.mm.; red blood cells nil; protein 100 mg. per 100 ml.; chlorides

650 mg. per 100 ml. No organisms were found in direct smear or culture.

On the morning after admission, the patient had a third fit lasting 1 minute. She was now deeply unconscious and very oedematous. The urinary output was satisfactory. The body temperature was 103·8° F. (39·9° C.), the pulse rate 150, and the respiratory rate 44 per minute. Because of the likelihood of cerebral oedema, 40 ml. of 50 per cent sucrose was given intravenously, without any improvement in the level of unconsciousness.

At 1.30 p.m. on 10th February, 1958, 19 hours after admission, profuse vaginal bleeding occurred. About 3 pints (1·7 litres) of blood were lost in as many minutes, accompanied by some vesicles of hydatidiform mole. Blood transfusion was started, as the patient's condition rapidly deteriorated. It was decided that, in spite of the difficulties involved, evacuation of the mole from below would have to be undertaken.

The patient being apparently moribund, rapid evacuation of huge quantities of mole was carried out with ovum forceps and Rheinstädter's curettes. The uterine cavity was the size of a 20-weeks pregnancy and was situated directly under the abdominal wall, a large fibromyomatous mass lying posteriorly. Ergometrine 1 mg. was given intravenously. At the conclusion of the operation the uterine cavity appeared to be empty and bleeding ceased. The total blood loss was estimated at 4 pints (2·3 litres). Four units of blood were administered. Examination of the mole tissue showed no foetus.

Following evacuation of the uterus unconsciousness was deep, there being no reponse to heavy sternal pressure. The corneal reflex was absent.

On the following day, the body temperature rose to 106° F. (41·1° C.). Considerable respiratory difficulty with cyanosis was present. Tracheostomy was therefore carried out (Mr. Oliver McCullen). Bronchial toilet, through the tracheostomy opening, produced large quantities of purulent sputum. This toilet was repeated every 10 minutes for the next 4 days, the patient being turned from side to side every 30 minutes.

The body temperature now rose to 107·6° F. (42° C.). On the suggestion of the consultant anaesthetist (Dr. John McCarthy) a modified cooling technique was used. The patient was allowed to lie naked on the operating table. Damp cloths were applied to the body surface and frequently renewed, while a domestic hair-drier was used to produce a draught.

By means of this crude method the body temperature was reduced to 98·4° F. (36·9° C.) in 3 hours. Thereafter, the patient was clad in a theatre gown, without bed-covers. The body temperature fell to 96° F. (35·5° C.) and remained at this level until bed-covers were replaced. No serious pyrexia recurred at any time thereafter.

The plasma proteins being very low, 1 unit (560 ml.) of reconstituted dried plasma was given following blood transfusion. Forty ml. of 50 per cent sucrose was repeated intravenously without noticeable effect on the degree of unconsciousness.

12th February, 1958. Fourth day of unconsciousness. The corneal and conjunctival reflexes were now present. The body temperature slowly rose to normal. Bronchial toilet was carried out through the tracheostomy tube every 10 minutes, or more frequently if the breathing became stertorous. Large quantities of muco-purulent material were removed by this means. The patient was changed from side to side at half-hourly intervals and pressure areas were treated hourly.

Feeding was started by Ryle's tube, calcium caseinate and beaten eggs being administered 4-hourly, with milk and water. A multi-vitamin preparation was given intramuscularly.

13th February, 1958. Fifth day of unconsciousness. The body temperature remained virtually normal. There was slight vaginal bleeding. Nursing attention was continued. Repeat of lumbar puncture revealed clear fluid under a pressure of 20 mm. of cerebrospinal fluid. The Queckenstedt test was again positive. Biochemical tests were normal apart from protein, which was raised to 70 mg. per 100 ml. The culture was again sterile.

14th February, 1958. In the early hours of the morning, consciousness was regained. Later in the day, the patient answered simple questions. Bronchial toilet was continued as necessary, and the patient was encouraged to cough.

Tube feeding was discontinued on the following day, as the patient was able to swallow. The tracheostomy tube was removed after 23 days and the fistula closed spontaneously about 10 days later.

The plasma protein level returned to 7 g. per 100 ml. after 3 weeks, the blood urea falling to 23 mg. per 100 ml. in the same time. A persistent *Escherichia coli* urinary infection responded eventually to suitable therapy. There was marked paresis of the left leg which responded slowly to physiotherapy.

Slight vaginal bleeding recurred and curettage was carried out on 20th March, 1958. The cavity of the uterus measured 4½ inches (11·25 cm.) and the uterus was the size of an orange. Multiple large fibromyomata were present and the ovaries were enlarged and cystic. Histological examination of the curettings was reported on as follows:

> "The curettings show some small pieces of endometrium in which no decidual reaction is apparent. There is one degenerate chorionic structure which shows an exuberant layer of trophoblast. Both syncytial and Langhans' elements are represented, and, while nuclear pleomorphism is not unduly marked, there is a moderate number of mitoses. The behaviour of the Hogben test would be of considerable importance. A reversion to a positive reaction would call for hysterectomy, though the case might prove to be a chorioadenoma destruens (malignant mole) rather than a true choriocarcinoma."

Accordingly, Hogben tests were carried out at fortnightly intervals. This test became negative 9 weeks after evacuation of the uterus but reverted to positive 10 weeks post-operatively. Chest X-ray was negative.

On 26th April, 1958, almost 11 weeks after admission, total hysterectomy and bilateral salpingo-oöphorectomy

was performed. There were multiple uterine fibromyomata and the uterus was the size of a 14-weeks pregnancy. There was a cyst 2 inches (5 cm.) in diameter in the right ovary. There was a little free fluid in the peritoneal cavity but no evidence of penetrating mole or of secondaries.

Pathological Report

"There is no evidence of choriocarcinoma or of retained vesicular mole in the uterine cavity. Naked-eye section of the uterus in a variety of planes shows a penetrating fragment of mole deep in the myometrium in the right cornual region. There is no associated haemorrhage.

"Microscopical examination confirms this. There are a number of hydatidiform villi with an exuberant trophoblastic covering. As in the case of the curetted material examined earlier, there is considerable nuclear pleomorphism in both the syncytial and Langhans' elements and there are moderate numbers of mitoses. The appearance is typical of malignant hydatidiform mole (chorioadenoma destruens)."

Post-operative recovery was completely uneventful, and the patient was discharged on the 18th post-operative day, following over 3-months stay in hospital.

20th August, 1958. Twenty-seven weeks after evacuation of the mole, the patient was seen again. She was in good general health, having gained 2 stones in weight since discharge. Pelvic examination revealed no abnormality. The blood pressure was 170/100. There was no proteinuria. There was slight paresis of the left leg, consisting mainly of foot-drop. The patient was able to do all her housework, however. The Hogben test was negative.

8th May, 1959. Fifteen months after evacuation of the mole, the patient was in very good health. Pelvic examination again revealed no abnormality. The blood pressure was 160/95 and there was no proteinuria. There was now no evidence of paresis, although some subjective weakness of the left leg remained. The Hogben test was negative.

Discussion

At the National Maternity Hospital, Dublin, during the 27 years, 1932–1958, 84 cases of hydatidiform mole were seen in 104,017 pregnancies, an incidence of 1 in 1,238. No maternal death occurred in these cases, and the case described above was the only one complicated by eclampsia. The above figures refer only to cases of total hydatidiform mole, minor degrees of hydatidiform degeneration not being included.

Chesley, Cosgrove and Preece (1946) recorded a case of eclampsia complicating hydatidiform mole, and, as result of a search of the literature, discovered 35 other cases of "probable or alleged eclampsia" in the same condition. Of the total of 36 cases thus collected, death occurred in 5, a mortality of 14 per cent.

Since the publication of the article by Chesley, Cosgrove and Preece, I have been able to discover only 7 further cases of this complication of hydatidiform mole in the literature, so that, including the case referred to in this article, the complication seems to have been reported 44 times only. The present case is the only one reported from the British Isles.

Acosta-Sison (1955) reported 2 cases in which death occurred in hydatidiform mole, both patients showing pathological signs of eclampsia at post-mortem. Neither of these patients had convulsions, however.

In the 2 cases reported by Ravina and Jamain (1944) and by Pigeaud (1949) a small macerated foetus was found as well as a large hydatidiform mole.

In the case reported by Mueller and Lapp (1949) 3 convulsions occurred on the 6th post-partum day in a patient who had been delivered of a hydatidiform mole by hysterotomy, hypertension, proteinuria and oedema being present.

Post (1959) describes a case of hydatidiform mole in which 1 eclamptic convulsion occurred. The case was dealt with by hysterotomy.

One of the 3 cases reported by Estrada Ocampo (1958) from Mexico is described as having had 18 fits in 12 hours. In the case described in the present paper 20–30 fits occurred and the patient was unconscious for 5 days.

Summary

(1) A case of eclampsia complicating hydatidiform mole is described. The patient was unconscious for 5 days, with hyperpyrexia.

(2) The case illustrates the value of tracheostomy in prolonged coma and of cooling in the treatment of hyperpyrexia.

(3) Seven cases of eclampsia in hydatidiform mole have been culled from the recent literature and these have to be added to the 36 cases reviewed by Chesley, Cosgrove and Preece.

Acknowledgments

I am grateful to Dr. C. F. V. Coyle, Master of the National Maternity Hospital, for permission to publish the case report. Mr. de Chezal kindly translated articles from the French, and Miss Ailbhe McMullin the article from Spanish. I am particularly pleased to record my gratitude to the librarian and staff of the Royal Society of Medicine, London. Nursing care was largely responsible for the recovery of the patient described in the case report; to Sister K. Donaghy and her nursing staff go congratulations and thanks.

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REACTIONS TO INTRAMUSCULAR IRON THERAPY IN ANAEMIA IN PREGNANCY

BY

M. K. KRISHNA MENON, B.A., M.D.
Director and Professor of Obstetrics and Gynaecology
Madras Medical College

AND

MARY WILLMOT, M.B., D.G.O.
Research Assistant

Institute of Obstetrics and Gynaecology, Government Hospital for Women and Children, Madras-8, India

A NEW iron-dextran complex Imferon has been described (Baird and Podmore, 1954; Cappell *et al.*, 1954; Scott and Govan, 1954). It is reported to be less toxic and more stable than saccharated iron oxide. Adequate serum concentrations have been obtained after the administration of this iron-dextran complex, the maximum absorption occurring in the first two days and the serum iron level falling to normal about the seventh day. Toxic reactions were not observed or, when present, were slight.

During a twelve-month period from August, 1958 to August, 1959, we treated 112 patients with anaemia in pregnancy using Imferon. Two types of anaemia are commonly encountered in pregnancy—the purely iron deficiency anaemia and the dimorphic variety which is due to a dual deficiency. The former responds to iron therapy especially parenteral and the latter to iron with folic acid or vitamin B_{12}. In this series there were 43 cases of iron deficiency anaemia (microcytic hypochromic) and 69 cases of dimorphic anaemia (macrocytic hypochromic with normoblastic or megaloblastic bone marrow). The scheme of giving iron was as follows:

The total iron deficit for each patient was calculated according to the formula suggested by the manufacturers of Imferon wherein both the body weight of the patient and haemoglobin level are taken into consideration. Imferon was then administered intramuscularly. In the earlier part of the study we gave 200 mg. intramuscularly daily till the deficiency was made up. But because of the reactions observed this dosage was reduced to 150 mg. daily and still later in the series to 100 mg. on alternate days. All patients in this study were admitted into hospital and were under the constant care of the same officer till discharge.

The duration of pregnancy ranged from 22 weeks to 36 weeks. In every case, in addition to the routine estimation of haemoglobin, enumeration of red cells, determination of packed cell volume and peripheral blood smear examination, bone marrow biopsies were done and serum iron and proteins estimated. Haematological investigations were repeated at weekly intervals except the bone marrow biopsy. Detailed records of all reactions noticed were maintained.

This paper deals with only the reactions noted in pregnancy resulting from intramuscular iron therapy. Only reactions severe enough to render the patient ill and bed-ridden are taken into consideration. Minor reactions like nausea, mild aches and pains and pain at the site of injection are not included.

Reactions

In this series of 112 pregnant patients reactions serious enough to invite special attention were seen in 19 patients—an incidence of 16·9 per cent. In all 1,482 injections were given to these 112 patients. The reactions noted are given below:

(1) Severe muscle and joint pains ..	18
(2) Encephalopathy	2
(3) Effusion into joints	2
(4) Cerebral haemorrhage	1
(5) Lymphadenitis and spots on skin	2
(6) Pyrexia	1

Muscle and Joint Pains

This has been the commonest manifestation—18 out of the 19 patients with reactions exhibiting it. All these patients were acutely ill, complaining of very severe pain mostly in the muscles of the calf and upper arm muscles. In almost all, the pain was bilateral. Tenderness of the muscles was extreme, patients resenting even gentle touch. They were unable to get out of bed and had to be fed and nursed in bed. Pain around the larger joints—knee, ankle and elbow—was invariably associated with the muscle pain. The smaller joints were however free of pain. All symptoms disappeared completely within 4–5 days of stopping the injections. Antihistaminics, vitamin B_1 and salicylates did not give these patients any relief.

Encephalopathy

During the course of treatment two patients developed symptoms suggestive of encephalopathy. A brief summary of the cases is given below to illustrate the reaction.

Patient M., aged 27 years, a 7th gravida was admitted into hospital in the 28th week of pregnancy. There was nothing significant in her previous obstetric or general history. General examination did not reveal any abnormality. Her blood pressure was 120/70 mm. Hg and urine was free of albumin. Her haematological data were as follows: haemoglobin 7·3 g. (14·5 g.=100 per cent), P.C.V. 29 per cent, M.C.V. 126 cu.μ., M.C.H.C. 25 per cent; total iron requirement 1,850 mg. and bone marrow was normoblastic.

She was diagnosed as a case of dimorphic anaemia. In addition to folic acid 15 mg. daily orally she was given injections of 200 mg. of Imferon daily. At the end of the eighth injection (i.e., after 1,600 mg. of Imferon) she developed acute pain and tenderness in the muscles of the calf and both arms. Two days later she became drowsy, resenting all interference.

She complained of severe pain all over the body. Her blood pressure rose to 200/110 mm. Hg but there was no albumin in the urine. Examination revealed rigidity of the neck muscles. Neurological examination however did not yield any positive signs. The optic fundi were normal. On lumbar puncture the cerebrospinal fluid was under pressure—110 drops per minute but clear. The rest of the findings in the cerebrospinal fluid were as follows: cells 50 per ml. (mostly lymphocytes); total proteins 76 mg. per cent, globulins one plus, chlorides 690 mg. per cent and sugar 63 mg. per cent. Culture and smear—no organism. Temperature was normal. She was kept on sedatives, the Imferon having been stopped at the onset of cerebral symptoms. She started to improve steadily but her blood pressure fluctuated between 160/100–180/120 mm. Hg and urine contained no albumin. Except for the fluctuating blood pressure she was perfectly normal and she went home against advice 10 days after the onset of the encephalopathy. On discharge her haemoglobin was 11·6 g. per cent. Three weeks later she came back in labour, delivered a dead-born child and went home on the 5th day. The blood pressure at this stage was 110/70 mm. Hg. There was no albumin in the urine.

The second case was a 9th gravida, 28-weeks pregnant with dimorphic anaemia. Haemoglobin 6·9 g. per cent, P.C.V. 25 per cent, M.C.V. 100 cu.μ., M.C.H.C. 27·6 per cent. Bone marrow—normoblastic. Total iron requirement 2,000 mg. She had in addition pre-eclamptic toxaemia. Blood pressure 190/144 mm. Hg; urine 2 plus—albumin, no casts, red cells or pus cells. She was treated for toxaemia on routine regime and for the anaemia she was given folic acid 15 mg. orally and Imferon 100 mg. daily. After 600 mg. of Imferon had

been given she developed severe pain in the muscles of the calf and arms followed two days later by drowsiness, neck rigidity, headache, and extreme bodily pain. Optic fundi were normal. Lumbar puncture showed cerebrospinal fluid under high tension. No cells, total proteins 56 mg. per cent (globulin negative), chlorides 630 mg. per cent, sugar 53 mg. per cent. Within four days of stopping Imferon her symptoms disappeared and she steadily improved. As the toxaemia failed to respond to treatment labour was induced two weeks later. She was delivered of a live child. On discharge a week after delivery her blood pressure was 110/80 mm. Hg. Urine free of albumin.

Comment

These two are cases of dimorphic anaemia. From our previous experience we are partial to the treatment of these cases with iron and folic acid. When the anaemia is severe and patient late in pregnancy we prefer parenteral iron. From 1952 we have treated a large number of this type of case with saccharated oxide of iron intravenously and folic acid orally. Except in a small number where we had immediate reactions in the form of collapse which responded quickly to resuscitation we never had the type of reactions seen in these two cases. Having treated a large number of patients with pre-eclamptic toxaemia we are of the opinion that symptoms noticed in these two cases cannot be due to pre-eclampsia. The fact that the patient recovered from the symptoms on stopping Imferon while the pre-eclamptic toxaemia symptoms persisted is sufficient proof and points to Imferon as the responsible factor. Could it be that parenteral iron should not be used in patients with pre-eclampsia? But why then did we not have the same experience with intravenous iron therapy?

Effusion Into the Joints

A 10th gravida in her 32-week of pregnancy was admitted for pre-eclamptic toxaemia and anaemia. Her blood pressure was 150/90 mm. Hg. Urine contained one plus albumin, no casts, red cells or pus cells. Haemoglobin 6 g. per cent; P.C.V. 23 per cent; M.C.V. 127·7 cu.μ.; M.C.H.C. 26 per cent and bone marrow was normoblastic. Total iron requirement 2,150 mg. She was treated with folic acid 15 mg. orally daily and Imferon 150 mg. on alternate days. She complained of severe pain in the right thigh and calf muscles after 250 mg. of Imferon. After she had 450 mg. of Imferon, she developed effusion in the right knee joint rendering all movements at the right knee painful and limited. All investigations to locate an organic lesion drew blank. Imferon was stopped. A week later the joint returned to normal; movements at the right knee were quite normal and no fluid could be detected in the joint. Radiography also showed a normal joint. Imferon was restarted, 100 mg. daily. On the second injection the swelling, effusion and pain in the right knee joint reappeared and in addition the right ankle also was similarly affected. Imferon was stopped. She rapidly improved. When 12 days later she delivered and went home the joints were functionally normal with no trace of effusion. Another patient with dimorphic anaemia developed effusion into the right ankle joint after receiving 250 mg. of Imferon in two injections. Antihistaminics and salicylates failed to relieve the joint pain and effusion. The Imferon however was continued. After another 150 mg. of Imferon, she developed swelling, pain and effusion into the left knee joint. The following day she developed swelling of the right knee and shoulder joints. No bony lesions were seen on X-ray examination of the joints. We persisted with the Imferon injection till the deficit of 1,550 mg. was given in 10 days. Her joint condition also persisted. Following the stopping of injection steady improvement in the condition of joints was noticed. Ten days after the stoppage of injection all affected joints were completely normal. On discharge her haemoglobin was 10·4 g.; at the start it was 6 g. per cent.

Cerebral Haemorrhage

We are constrained to report this case in detail. Mrs. P., a 7th gravida aged 32 years, with a good obstetric and general medical record, was admitted into the hospital with symptoms of

threatened abortion at the 12th week of her present pregnancy. Routine examination did not reveal any abnormality except that her haemoglobin was 8·7 g. per cent. There was no albumin in the urine and blood pressure was 96/60 mm. Hg. After a few days rest in bed which relieved all her symptoms she was discharged with a request to attend the antenatal department regularly and advised to take iron orally—ferrous sulphate 5 grains three times a day. She attended regularly but it was gathered she did not take the prescribed iron regularly. However, near term, 38 weeks, she developed swelling of the feet and she was admitted into hospital. Examination revealed a uterus nearly full term, live foetus presenting by the vertex (L.O.A. position) with the head floating. Her blood pressure was 120/70 mm. Hg; pulse 70, urine contained no albumin. Detailed haematological investigations revealed: haemoglobin 7·6 g. per cent, P.C.V. 25 per cent, M.C.V. 125 cu.μ., M.C.H.C. 30 per cent. Total iron requirement 1,850 mg. Bone marrow biopsy revealed a megaloblastic picture. Serum iron 35·7 micrograms per cent. Electrophoretic pattern of serum proteins in grams per cent: total proteins 5·25, albumin 1·90, globulin 3·35, alpha$_1$ 0·53, alpha$_2$ 0·59, beta 105, gamma 1·58.

The calculated iron deficit of 1,850 mg. was then given to the patient from the third day of admission onwards in doses of 100 mg. daily for two days and, since there was no reaction, the rest of the deficit was given to her in daily injection of 200 mg. of Imferon. Because of the dimorphic nature of the anaemia she was also given 30 mg. of folic acid daily by mouth. Seven days after admission, by which time she had 1,000 mg. of Imferon, she delivered naturally of a live healthy baby with a haemoglobin level of 18·4 g. per cent and a serum iron level of 142·8 micrograms. The rest of the iron deficit was given in the same way in the puerperium, the whole of 1,850 mg. deficit being given in 12 days from the start of treatment. On completion of treatment her haemoglobin level was 8·3 g. per cent and serum iron 128·6 micrograms per cent. The serum protein values in grams per cent were: total proteins 5·25, albumin 2·25, globulin 3·01, alpha$_1$ 0·58, alpha$_2$ 0·68, beta 0·68 and gamma 1·03. Her condition was satisfactory. Her blood pressure was 110/70 mm. Hg, there was no albumin in the urine and the puerperium was apyrexial. She went home a week after delivery.

Six days later she was re-admitted with a history of having suddenly become unconscious 12 hours prior to admission. Till this attack, since her discharge from hospital she had been keeping well and fit. Physical examination made a diagnosis of a cerebral vascular accident almost a certainty. Her blood pressure was 170/100 mm. Hg, pulse 54 per minute and temperature 98·4° F. Urine contained 2 plus albumin with leucocytes, red cells and casts. Haematological examination: haemoglobin 9·7 g. per cent, R.B.C. 2·5 millions per c.mm., W.B.C. 12,800, P.C.V. 25 per cent and serum iron 128·5 micrograms. The cerebrospinal fluid on lumbar puncture was uniformly blood stained but not under marked tension. Microscopically there were 90 cells per c.mm., mostly lymphocytes. Biochemical analysis revealed: proteins 53 mg., globulin one plus, chlorides 750 mg., sugar 63 mg. and blood urea was 14 mg. per cent.

A diagnosis of cerebral haemorrhage was made. Eight hours after admission she had three generalized convulsions and she died 21 hours after admission.

Post-mortem Findings

All tissues in addition to routine staining were also specifically stained for iron. In the brain there was a large blood-clot extending from the lateral ventricles to the third and fourth ventricles (Fig. 1). As the ventricles were filled with blood-clot the site of haemorrhage could not be located. Brain sections stained for iron were negative. There were few small areas of haemorrhage on the inner surface of the dura over both temporal lobes. These areas of haemorrhage showed iron deposits. The eyeballs showed scattered areas of iron granules over a small surface of the retina. There were no arterio-sclerotic changes in the vessels. The kidneys weighed 93 g. each. They were normal on gross examination. The capsule of the kidneys stripped easily. There was no con-

gestion. The cut section appeared normal. Microscopic examination: there was appreciable variation in the size of the glomeruli, a small number of them appearing shrunken. The outline of capillary tufts was well preserved. Fair-sized brown pigment granules were seen in the endothelial lining of the capillary loops of almost all the glomeruli. The blood vessels of the medulla were congested and the epithelium of the proximal convoluted tubules showed early degenerative changes not amounting to necrosis. The blood vessels were normal. The pigment granules on specific staining were positive for iron (Fig. 2). The renal artery stained for iron was negative. The bone-marrow when stained for iron did not show any deposits. The lungs were normal on gross examination and weighed 1,305 g. Microscopic examination showed congestion and pulmonary oedema. Sections stained especially for iron were negative. The spleen weighed 192 g., showed congestion on microscopic examination and a few iron deposits when stained for iron. The liver weighed 1,305 g. and showed congestion and fatty change. There were no iron deposits on special staining. The uterus, ovaries, pituitary, adrenals, pancreas and heart did not show any abnormalities. In the small intestines there were areas of bile-staining together with areas of congestion and small punctate haemorrhage. When stained for iron these areas of haemorrhage were negative. *Cause of death:* ventricular haemorrhage most probably due to acute hypertension resulting from the toxic effects of iron on the kidney.

Comment

At no time during her pregnancy and puerperium did this patient have any raised blood pressure or albumin in urine nor any reaction to Imferon. As such when she was re-admitted six days after delivery with coma we thought of the possibility of cerebral venous thrombosis of the puerperium also. It was only on autopsy that the true nature of the lesion was revealed. Frank haemorrhage into the ventricles confirmed the diagnosis of cerebral haemorrhage as the cause of death. We specifically stained all tissues for iron, for as far back as 1921 Steigler had shown that injected iron could be deposited in the kidney. The presence of a large amount of iron in the glomerular endothelial cells led us to conclude that most probably as a result of the kidney damage resulting from injected iron an acute hypertension resulting in cerebral haemorrhage caused the death of the patient. Except for anaemia this patient had maintained good health all through her pregnancy. As mentioned before at no time during this pregnancy did she have any elevated blood pressure or albumin in the urine. Clinically at least she did not exhibit any sign or symptom at any time during pregnancy of cardiovascular or renal disease. After her delivery on discharge also the blood pressure was normal and urine free of any albumin. Therefore it is hard to believe that the cerebral haemorrhage she died from is not in any way connected with the finding of iron deposits in the glomeruli. It would appear that in this patient the iron in circulation got deposited in the glomeruli resulting in an acute hypertension sufficient enough to produce haemorrhage into ventricles by rupture of the vessels.

Muscle and Joint Pain Associated with Pigment Spots (2 Cases)

One case is reported to illustrate the reaction. Patient L., 30 years, a second gravida was admitted in the 36th week of pregnancy with anaemia. Haemoglobin was 2·8 g.; M.C.V. 130 cu.μ.; M.C.H.C. 20 per cent. Bone-marrow: normoblastic and iron requirements 2,650 mg. Patient was started on Imferon. After 750 mg. of Imferon the patient complained of muscle and joint pain in the lower limbs. Two days later, after 950 mg. of Imferon, a few reddish spots were observed on both calf muscles. They were slightly raised, not tender, margins were well-defined and there was no blanching on pressure. Imferon was stopped. The spots, muscle and joint pain subsided within four days. Imferon was restarted. After 150 mg. of Imferon the muscle and joint pain in both lower extremities reappeared and large numbers of pigmented spots were observed all over both the lower limbs below the inguinal ligament. Imferon was continued. The muscle and joint pain spread to involve the upper limbs and neck but no spots

FIG. 1
Section of brain showing haemorrhage into the ventricles.

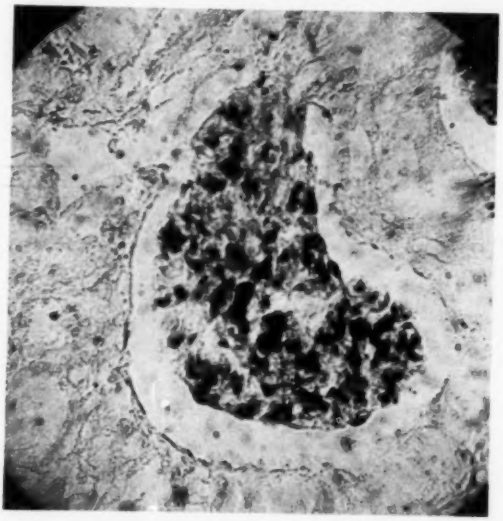

FIG. 2
Section of a glomerulus specifically stained for iron. Note the heavy darkly staining pigment granules. ×320.

were noticed above the inguinal ligament. The inguinal glands on both sides became enlarged and tender. The muscle and joint pain persisted but the pigmented spots began to disappear gradually after 48 hours. As the patient looked ill, Imferon was stopped after 2,150 mg. After the drug was discontinued the patient rapidly improved and returned to normal within a week. A skin biopsy was done from pigmented areas and control sections were taken from the normal skin of the fore-arm. The pigmented areas of the skin showed no vascular disturbances like congestion or haemorrhage. When sections were stained for iron they showed areas where iron was deposited immediately beneath the surface epithelium either as fine granules or as ill-defined areas of pigmentation staining faintly and diffusely. This pigmentation appeared to surround one or more vascular channels, probably the lymphatics. Such areas were not evident in the control section of the skin of the fore-arm.

Staining of the skin is said to be an annoying feature of Imferon injection. Out of 1,482 injections given to 112 patients we observed staining at the site injection in only two cases.

Other Observations

Of the 19 cases showing toxic reaction, 17 belonged to the group of dimorphic anaemia while among the purely iron deficiency group only 2 showed serious reactions. Thus in this series, in 69 cases of dimorphic anaemia reactions were observed in 17—an incidence of 27 per cent—while in 43 cases of iron deficiency anaemia reactions were observed in 2—an incidence of 4·6 per cent.

The average weight of the patients who developed reactions was 98 pounds while the average weight in the group which did not develop reactions was 101 pounds, there being no significance.

Toxic reactions appeared at any time during treatment. We did not have a single immediate reaction. We did not find any relationship between the amount of Imferon given and the development of reactions nor did we find any relationship to the daily dosage given. Patients who have been on 100 mg. on alternate days as well as those with 200 mg. daily have developed the same type of reactions. Nor did we find any relationship with the severity of the anaemia. The reactions have been noted in patients with as low haemoglobin as 2·5 g. per cent as in those with 7·6 g. per cent.

We have estimated in all cases the serum proteins, albumin and globulin and its various fractions α_1, α_2, beta and gamma by electrophoresis. We have found no significant difference in the total protein or its fractions in the group which developed reactions and in those which did not. For clarification we give below the range of haemoglobin and protein values in the cases which developed reactions and those which did not (Table I).

Table I

Group	Haemoglobin in g. Per cent	Average Serum Proteins in g. Per cent							
		Total	Albumin	Globulin	α_1	α_2	Beta	Gamma	A/G
No reactions ..	1·7–7·8 (range) 5·14 (average)	5·58	2·32	3·25	0·43	0·65	0·84	1·24	1:1·3
Reactions ..	2·5–7·6 (range) 5·3 (average)	5·44	2·09	3·41	0·42	0·62	0·911	1·45	1:1·7

Discussion

Innumerable reports are available on the efficacy of Imferon in the treatment of iron deficiency anaemia. We do not propose to discuss the efficacy at this stage as it will be the subject of another communication. But we make this statement that we are in general agreement with certain reservations with the published reports regarding its efficacy.

Toxic reactions to Imferon are said to be negligible. Dempster *et al.* (1954) encountered local reactions in several patients and had to stop treatment in 2 of their 16 patients. Callender and Smith (1954) encountered 4 severe reactions in a limited period: 2 of these occurred soon after injection and 2 showed a delayed reaction of an allergic character. They gave the patients iron and dextran separately without producing any reactions and suggested that the combination of iron and dextran may result in a sensitizing compound. Jennison and Ellis (1954) reported mild reactions, including nausea, vomiting, depression, fainting in 20 per cent of these patients. Librach (1953) considers allergy to be an important factor especially in the production of early reactions and believes it may be due to natural hypersensitivity. Bourne (1955) reported a delayed reaction of a very serious nature after Imferon. Scott (1956), in a series of 300 patients, reports only 4 cases of toxic reactions.

From the brief summary of the literature it is evident that most of the reactions noted are not of a serious nature and that iron-dextran complex may present us with a combination of early and late reactions. We are now reporting a set of reactions which are serious. The commonest of these, namely the muscle and joint pains, completely incapacitate the patient and she is in distress. Encephalopathy occurred in 2 cases and 1 case of cerebral haemorrhage ended fatally. Effusion into joints which occurred in 2 cases also gave us some anxiety.

Curiously enough we found that in the non-pregnant these reactions were minimal. An analysis of 75 patients—admitted for gynaecological complaints—who were treated with Imferon showed that in 3 per cent of cases only reactions demanding attention were noticed. All of them were in the form of severe muscle and joint pains and joint effusions. We are thus led to conclude that Imferon gives rise to more severe and frequent reactions in pregnant women than in the non-pregnant; we also find that reactions were more common in the dimorphic type of anaemia and also that when pre-eclamptic toxaemia complicated anaemia Imferon gave rise to toxic reactions more frequently. Of 16 patients in this series who had toxaemia in addition, 8 developed serious reactions.

Since 1952 we have used iron intravenously (saccharated oxide of iron) in very similar cases —iron deficiency anaemia, and dimorphic anaemia in pregnant women with and without toxaemia. Except for the immediate reaction of shock and collapse in a few cases the reactions of the type met with after using Imferon were not encountered even in a single case. What is it then that makes the pregnant woman more sensitive to Imferon? If it is the iron moiety then it is only reasonable to presume that she should show the same type of reaction with intravenous iron. There is however this difference in the compound—one is iron dextran, the other is saccharated oxide of iron. Could it be that the combination of iron and dextran may result in a sensitizing compound as suggested by Callender and Smith (1954) and that pregnant women are more sensitive to this compound?

Most of the reports on the use of Imferon in pregnancy are based on treatment of cases with pure iron deficiency anaemia in pregnancy. The dimorphic type of anaemia which is common here is rare in countries from where these reports have emanated. The fact that reactions are more common in the latter variety of anaemia is worthy of note. And this in our opinion may explain the difference in the incidence and type of reactions noticed.

It has been suggested that the low serum proteins and alteration in albumin and globulin ratio may give rise to more frequent reactions with parenteral iron. In this institution the average serum proteins determined by electrophoresis in normal pregnant women in the last trimester is 6·46 g. per cent; albumin 2·44 g. per cent, globulin 4·02 g. per cent (Menon *et al.*, 1958). In anaemia the proteins fall still

lower. If it is unsafe to give parenteral iron when serum proteins are low it stands to reason that parenteral iron should be rigidly restricted in its use in countries like India where protein deficiency is so common. However from our experience with intravenous iron therapy in a large number of pregnant women with severe anaemia we have not been able to confirm this suggestion. All that we found was that when serum proteins were low the response to parenteral iron therapy was delayed.

Our main problem at present is anaemia and toxaemia. Patients come late in pregnancy with haemoglobin levels so low that we dread the onset of labour in them. Oral iron in our opinion has very little place in such cases. Blood transfusion is not without its danger either. Hence our treatment of choice is parenteral iron—intravenous or intramuscular.

From our experience we are constrained to admit that while satisfactory haematological response can be obtained by Imferon it is not without risk. In pure iron deficiency anaemia it may be fairly safe. But where the anaemia is dimorphic or when pre-eclamptic toxaemia complicates the anaemia we are now rather hesitant to use it. We are reluctant to use it in out-patients during pregnancy as recommended by many and we strongly recommend that its use be withheld until all investigations are completed and the anaemia proved to be pure iron deficiency anaemia.

Summary and Conclusions

One hundred and twelve pregnant women suffering from anaemia were treated with Imferon. Of these 43 were iron deficiency anaemia and 69 dimorphic anaemia. In 16 pre-eclamptic toxaemia was present in addition.

Nineteen patients developed serious reactions —an incidence of 17 per cent. The commonest type of reactions was severe muscle and joint pains. Two patients had encephalopathy, two joint effusions and one patient died of cerebral haemorrhage.

Reactions were more common and severe when the anaemia was dimorphic and when pre-eclampsia was present in addition.

We did not find any relationship between the severity of anaemia, the dosage of Imferon, the serum proteins and the incidence of reaction.

We found the reactions more common in pregnant women than in the non-pregnant.

It is concluded that in pregnancy Imferon should be used with great caution.

We are grateful to Messrs. Bengers Ltd. for helping us with a generous supply of Imferon while carrying out these trials. When we lost one patient from cerebral haemorrhage we sent to their laboratories at their request tissue blocks of the brain, kidneys, liver, etc., seven months ago. We await their reports.

We express our indebtedness to Mr. N. Ramaswamy, M.Sc., Biochemist and Dr. B. M. Venugopala Shetty, M.D., Associate Professor of Pathology (Gynaecology) at this Institute for their valuable help.

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TOXAEMIA OF PREGNANCY AND OBESITY

BY

ALICE STEWART, M.D., F.R.C.P.

AND

DAVID HEWITT, M.A.

From the Department of Social Medicine, Oxford University

THE purpose of the present investigation was to discover whether and to what extent obesity predisposes to toxaemia of pregnancy. It was based on routine antenatal records which described 2,522 mothers who had four things in common; they had recently given birth to a single child; they were systematically screened for toxaemia during the second half of this pregnancy; their heights were recorded and they had been weighed at least once in the non-pregnant state. Some of the records came from antenatal clinics in Northamptonshire and some from clinics in Surrey.

The Northamptonshire records were originally compiled during 1952 and have been described elsewhere (Clokie, 1959). In this more or less random series, which included all mothers with the necessary records (1,228), the weights were ascertained six to eight weeks after delivery.

The Surrey records were originally compiled during 1955–56 and were later collected by the Public Health Department (Soutar, 1959) for the purpose of comparing all premature births (i.e., under 5½ pounds) with an equal number of controls (over 5½ pounds). From this non-random set of records we obtained 1,294 mothers (643 from the premature and 651 from the control group) with "stated" pre-pregnancy weights and 818 mothers (402 from the premature and 416 from the control group) who were weighed again six to eight weeks after delivery.

In each series we have used as the yardstick of obesity the height (in inches) divided by the cube root of the weight (in pounds). This $H \div \sqrt[3]{W}$ index (H/W for short) distinguishes between women who were over or under weight for their height but needless to say does not distinguish between fat and other tissues. We shall, however, assume that the women with high indices (over 13·2) were always thin and that women with low indices (less than 12·0) were usually obese.

A diagnosis of toxaemia was based on blood pressure readings and other entries in the antenatal notes and if the appropriate records were missing the case was discarded. Each individual included in the investigation was placed in one of the following toxaemia grades:

Toxaemia		Antenatal Records		No. of Cases
Grade	Description	Stated Toxaemia	Maximum Diastolic Blood Pressure (mm. Hg)	
4	Definite	Yes	Unrestricted	367
3	Possible	No	Over 95*	71
2	Possible	No	90–95	292
1	Unlikely	No	81–89	458
0	Nil	No	80 or less	1,334

* Cases with transient albuminuria or oedema with blood pressures below 95 mm. were placed here.

We shall in the first instance compare cases of toxaemia diagnosed at the time (grade 4) with the other cases (grades 0–3), and describe the H/W indices based on pre-pregnancy weights. As these were only recorded in the Surrey data we shall be dealing first with the non-random group (i.e., a group containing an exceptionally large number of premature deliveries).

Pre-pregnancy Assessments of Obesity

The 1,294 Surrey mothers with stated pre-pregnancy weights were divided into two parity and two toxaemia groups with the following results:

Parity	Grade 4 Toxaemias	Other Grades
Primiparae ..	129	412
Multiparae ..	85	668

The H/W distributions of these 214 cases of toxaemia (grade 4) are shown in Table I (primiparae) and Table II (multiparae). In both tables the observed number of grade 4 toxaemias in six H/W categories are compared with the numbers which would be expected if there were

TABLE I

Body-build Distribution of Grade 4 Toxaemias. Pre-pregnancy Weights (Primiparae)

Body-build Scale $H \div \sqrt[3]{W}$	Population at Risk			Grade 4 Toxaemias			
				Prematures		Controls	
	Surrey Prematures No.	Surrey Controls No.	Estimated* %	Observed	Expected*	Observed	Expected*
10·6–12·1	37	23	9·25	12	7·96	6	3·98
–12·4	32	40	15·33	14	13·18	11	6·59
–12·7	51	48	18·69	13	16·07	13	8·04
–13·0	70	63	24·60	18	21·16	7	10·58
–13·3	47	44	17·14	15	14·74	2	7·37
–14·5	48	38	15·00	14	12·90	4	6·45
Total	285	256	100·01	86	86·01	43	43·01

* See text. In the estimated populations at risk it was assumed that the proportion of premature births was slightly higher for primiparae than for multiparae.

TABLE II

Body-build Distribution of Grade 4 Toxaemias. Pre-pregnancy Weights (Multiparae)

Body-build Scale $H \div \sqrt[3]{W}$	Population at Risk			Grade 4 Toxaemias			
				Prematures		Controls	
	Surrey Prematures No.	Surrey Controls No.	Estimated* %	Observed	Expected*	Observed	Expected*
10·6–12·1	40	54	13·54	13	8·93	4	2·57
–12·4	43	71	17·64	16	11·65	2	3·35
–12·7	68	78	19·71	14	13·01	1	3·74
–13·0	71	91	22·86	12	15·09	9	4·34
–13·3	80	61	15·82	7	10·44	2	3·01
–14·5	56	40	10·43	4	6·88	1	1·98
Total	358	395	100·00	66	66·00	19	18·99

* See text, also footnote to Table I.

no association between body build and toxaemia. As the incidence of toxaemia is influenced by parity and by maternal size, and as both of these also influence the prematurity rate, we have based our expectations on an imaginary "population at risk" whose body-build distribution approximates to what would have been found if the Surrey data had, as in the case of Northamptonshire, described a random sample of single deliveries. This imaginary population included 6 per cent of mothers from the premature group (the premature rate for Surrey in 1956 was exactly 6 per cent) and 94 per cent of mothers from the control group, and the expected numbers of toxaemia cases in Tables I and II are based on this population. As, however, the tables also show the H/W distributions of the original premature and control groups the reader is free to base his expectations either on the original groups or on the "estimated population at risk".

Whichever standard of comparison is used there appears to be a significant excess of grade 4 toxaemias with low H/W indices (obese end of the scale) and a significant deficit with high indices (thin end of the scale).

The strength of this association is shown in Table III where the "estimated" populations at risk are divided into two halves, according to whether the value for $H \div \sqrt[3]{W}$ lies above or below the median value for the group as a whole (12·7). In this table the ratios of actual to expected numbers of grade 4 toxaemias are given for 8 groups, also the quotients for four pairs of ratios (relative risks). It will be seen that the risk of toxaemia in the control group (which approximates most closely to a random sample of all pregnancies) was (1·31–0·74) or 1·77 times greater for the overweight half of the population at risk than for the underweight half. The corresponding figures for the atypical samples of primiparae (1·51) and multiparae (1·38) and for the premature group (1·35) show that the association between obesity and toxaemia holds for first pregnancies as well as for later pregnancies also for pregnancies which terminate prematurely as well as those which succeed in running to term.

TABLE III

Relative Risk of Toxaemia in Overweight and Underweight Halves of the Surrey Population at Risk
(see text)

Sub-groups	Grade 4 Toxaemias Ratio of Observed to Expected Numbers		Relative Risk of Toxaemia A÷B
	A*	B*	
Controls ..	1·31	0·74	1·77
Prematures	1·16	0·86	1·35
Primiparae	1·24	0·82	1·51
Multiparae	1·16	0·84	1·38

* A="overweight" half of the population at risk, $H \div \sqrt[3]{W}$ range=10·6–12·7.
B="underweight" half of the population at risk, $H \div \sqrt[3]{W}$ range=12·71–14·5.

The risks associated with more extreme deviations from normal build are demonstrated in Figure 1, where the percentage ratios between observed and expected numbers of grade 4 toxaemias are shown in six H/W categories (broken line). The only suspicious deviation from a straight line relationship between body-build and toxaemia is the point which corresponds to the highest H/W index (13·5). Within the normal range of body-build there appears to be a doubling of the toxaemia risk. This implies that, other things being equal, a woman of average height (64 inches) who weighed 11½ stones would be twice as likely to develop toxaemia as a woman of the same height who only weighed 8 stones. As, however, the heavier woman's chances of producing an undersized baby are below average, she might, on balance, run no greater risk of an unsuccessful pregnancy than the lighter woman. The well-known association between maternal size and size of the baby is also shown in Figure 1, where the risk of prematurity for different H/W categories is indicated by the continuous line. This estimate of risk is based on the Surrey data and shows that in respect of prematurity women who were under weight for their height compared unfavourably with women who were over weight.

POST-PREGNANCY ASSESSMENTS OF OBESITY
(Northamptonshire data)

A not infrequent consequence of the pre-eclamptic state is an excessive gain in weight

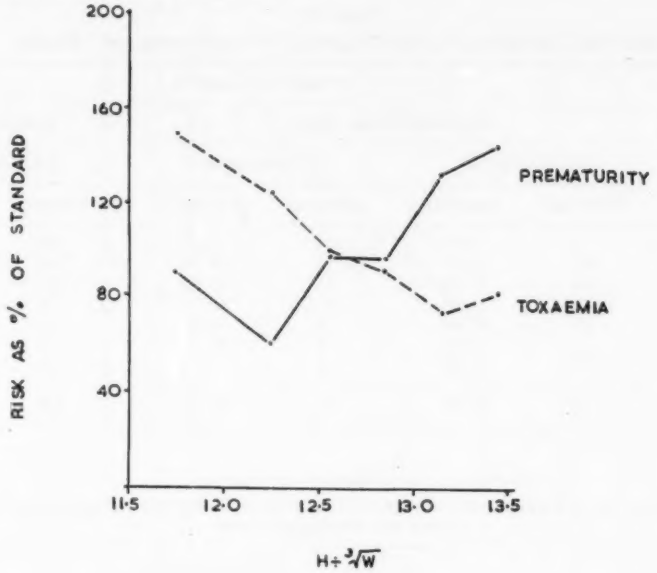

FIG. 1

Relationship between maternal physique and two obstetrical hazards (Surrey data).

towards the end of pregnancy. Most if not all of the extra weight is due to oedema, but the possibility of toxaemia resulting in a more permanent gain in weight must be considered. Fortunately a sufficiently large number of women in the Surrey survey had been weighed before conception and after delivery to show that the average weight changes were almost exactly the same for the women who were classified as grade 4 toxaemias as for the other women. In both series the average post-pregnancy weight was greater than the average pre-pregnancy weight, but the difference for the grade 4 toxaemias (5·71 pounds) was only a fraction greater than the difference for other women (5·68 pounds). When, in fact, the post-pregnancy weights of the Surrey mothers were used to calculate the relative risk of toxaemia in the overweight half of the population at risk, a figure of 1·36 was obtained which approximated closely to the figure (1·45) based on the pre-pregnancy weights. It was, therefore, decided to include the Northamptonshire data (which were randomly distributed in respect of parity and birth-weight) in the present investigation.

Once again the observed and expected numbers of grade 4 toxaemias for different values of $H \div \sqrt[3]{W}$ were ascertained and used to compare the toxaemia risk in the over- and underweight halves of the population at risk (see Tables IV and V). The resulting relative risks (2·29 for primiparae and 2·55 for multiparae) were appreciably higher than the corresponding ones obtained from the Surrey data, but as already stated it is more appropriate to compare the figure for Surrey controls (1·77) with the figure for all Northamptonshire women (2·36). The difference between these two figures could either be due to chance or to unrecognized differences between the two areas and the two periods.

TABLE IV

Body-build Distribution of Grade 4 Toxaemias. Pre- and Post-pregnancy Weights

Body-build Scale $H \div \sqrt[3]{W}$	Grade 4 Toxaemias					
	Northamptonshire Data				Combined Data	
	446 Primiparae		782 Multiparae		2,522 All Parities	
	Observed	Expected	Observed	Expected	Observed	Expected
10·6–11·8	8	4·78	15	6·81	43	22·31
–12·1	11	6·43	12	6·36	38	25·51
–12·4	18	11·95	12	12·80	73	59·52
–12·7	18	15·44	17	16·25	76	72·55
–13·0	12	19·49	7	12·53	65	83·19
–13·3	5	13·24	5	10·99	36	59·79
–14·5	10	10·66	3	5·27	36	44·14
Total	82	81·99	71	71·01	367	367·01

TABLE V

Relative Risk of Toxaemia in Overweight and Underweight Halves of the Population at Risk
(Surrey and Northamptonshire)

Region	Parity	Grade 4 Toxaemias		Relative Risk of Toxaemia
		Ratio of Observed to Expected Nos.		
		A*	B*	A–B
Northamptonshire	Primiparae ..	1·42	0·62	2·29
	Multiparae ..	1·33	0·52	2·55
Northamptonshire and Surrey ..	All parities ..	1·28	0·72	1·75

* A = "overweight" half of the population at risk $H \div \sqrt[3]{W}$ range = 10·6–12·7.
B = "underweight" half of the population at risk $H \div \sqrt[3]{W}$ range = 12·71–14·5.

COMBINED DATA

The last column of Table IV shows the aggregate figures for observed and expected grade 4 toxaemias in the two samples, and Figure 2 shows the corresponding percentage ratios after standardization for region and parity. Within the $H \div \sqrt[3]{W}$ range of 11·5 to 13·3 toxaemia risk appeared to be a linear function of body-build but, once again, the number of toxaemia cases (36) in the thinnest body-build group was considerably greater than would be expected from the projection of a straight line based on the other six points. This latter finding suggests that there may be, in respect of toxaemia, an optimal physique which roughly corresponds to a $H \div \sqrt[3]{W}$ value of 13·3. For a woman of average height this requires a weight of 8 stones, or about one stone lighter than the average weight for this height.

OTHER GRADES OF TOXAEMIA

Thus far we have been content to compare the physique of mothers who were known to have toxaemia with the physique of all other mothers. But it is reasonable to suppose that a few missed cases were included in the intermediate grades (1–4). We have therefore, ascertained the proportion of mothers with

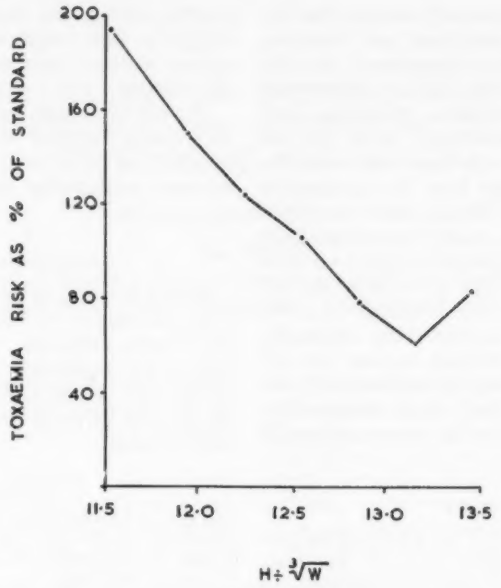

FIG. 2

Relationship between maternal physique and toxaemia of pregnancy (combined data).

H/W indices above and below 12·7 in each toxaemia grade:

Toxaemia Grade	Ratio of Overweight to Underweight Mothers	No. of Cases
0	0·84	1,334
1	0·82	458
2	0·98	292
3	1·09	71
4	1·75	367

The tendency for women who do not suffer from toxaemia to be below average weight for their height is shown by the low ratio (0·84) for grade 0. As a similar ratio was obtained for grade 1 (0·82) it is unlikely that there were any missed cases of toxaemia in this group. The same cannot be said of grades 3 and 4, but there is no reason to think that the number of missed cases was large.

DISCUSSION

There is nothing new in the discovery that exceptionally obese women are a poor risk from the point of view of toxaemia of pregnancy (Møller-Christensen, 1938; Koller and Zoller, 1941; von Biro, 1944), but it does not appear to have been recognized that the optimal physique in respect of toxaemia is well on the thin side of normal. This is presumably because earlier workers ignored the height component of weight and were content to compare exceptionally heavy women with so-called normals.

We appear to have ignored the possibility that the observed association between obesity and risk of toxaemia is spurious and merely due to the fact that both are associated with age. But in fact the extent of this bias was investigated and was found to be negligible. We realize that the weights which we have quoted are only approximate ones and that we do not even know whether they were taken dressed or undressed.

There is, however, no reason to suspect that the relationship between body-build and toxaemia of pregnancy has been exaggerated on this account. On the contrary, if, as undoubtedly was the case, some mothers overstated their weights and others understated them, the true relationship between body-build and toxaemia is bound to be stronger than the relationship we have demonstrated. What is more, even if the risk gradient had been exactly determined (and had in consequence appeared steeper) we have still understated the role of obesity in the aetiology of toxaemia. For although the H/W index identifies thin women fairly efficiently, it cannot distinguish between women who are over weight because they are exceptionally fat and women who are over weight because they are exceptionally muscular or have exceptionally thick bones.

Summary

Body-build indices ($H \div \sqrt[3]{W}$) based on pre- and post-pregnancy weight records were obtained for 2,522 mothers who were also screened for toxaemia.

The incidence of toxaemia was higher than average among the mothers who were over weight for their height and lower than average among mothers who were under weight for their height.

The relatively high toxaemia risks associated with obesity applied to first and later pregnancies, and also to pregnancies which terminated prematurely and pregnancies which ran to term.

Acknowledgments

We are indebted to Dr. C. M. Smith, Medical Officer of Health for Northamptonshire, and to Dr. Soutar, Medical Officer of Health for Surrey, foı supervising the field work for this survey and for allowing us to examine data which were collected mainly by midwives and health visitors.

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FURTHER STUDIES ON THE RELIABILITY OF A NEW METHOD FOR THE DETERMINATION OF THE DURATION OF PREGNANCY

BY

SAM BRODY

Department of Women's Diseases, Karolinska Sjukhuset, Stockholm and King Gustaf V Research Institute, Stockholm, Sweden

THE precise determination of the duration of pregnancy is still an unsolved problem and the inadequacy of conventional methods is generally agreed upon.

In clinical work the assessment of gestational age is based either on the menstrual history of the mother or on certain morphological characteristics in the newborn infant. The first-mentioned method is a subjective approach and is, moreover, very often based on unreliable data. Deviations from the computed confinement date are numerous and sometimes very considerable.

A rational attack on the problem was originally induced by medico-legal demands for an objective appraisal of the duration of pregnancy. It is obvious, however, that precise age-determination is of more general medical interest. Particularly during the last few years the need for accurate methods has been actualized by problems concerned with neonatal morbidity and mortality. The physiology and pathology of the foetus during late pregnancy has lately attracted considerable interest both from obstetricians and paediatricians. New concepts have been introduced and entities such as, e.g., postmaturity and the placental insufficiency syndrome are now commonly discussed.

The relation of these pathological states to the duration of pregnancy is, however, not well defined, obviously owing to the lack of precision in the determination of the gestational age with conventional methods.

As is evident from the literature, the morphological characteristics, which form the basis of our present objective age-determination methods, are subject to very large individual variations. This, of course, will inevitably introduce an error when these factors are employed as indices of the duration of pregnancy and the considerable scatter renders calculations based on these data highly uncertain.

The above considerations emphasize the need for a radically new approach to the problem. From a realization of the inadequacy of the morphological characteristics as criteria of foetal maturity it is natural to proceed to the assumption that functional characteristics of foetal development might more closely reflect the intra-uterine age. A logical continuation of this line of thought is to search for physiological or biochemical data that are correlated to the functional maturation of the foetus and that might provide a basis for a new technique for the determination of the duration of pregnancy.

THE APPROACH

The foetal haemoglobin has attracted some interest during the last decade as a possible index of the degree of maturity of the newborn and as a measure of the duration of pregnancy. A review of the literature has been given elsewhere (Brody, 1960). The finding that the adult type of haemoglobin is produced quite early in intra-uterine life (Beaven, Hoch and Holiday, 1951; Walker and Turnbull, 1955), causing a gradual change in the proportion of the two types of haemoglobin, was the impetus for attempts to correlate the proportion of foetal

haemoglobin with the gestational age. Although a relationship between these parameters has been established, considerable individual variations in the proportion of foetal haemoglobin reduce its value as an accurate index of the duration of pregnancy (Brody, 1958; Gerbie, DeCosta and Reis, 1959).

As a result of a systematic analysis of the relationship between weight, length and proportion of foetal haemoglobin of the newborn and the post-menstrual duration of pregnancy the present author found that all these characteristics had approximately the same standard error of estimate (Brody, 1958). The same rather low precision was thus found in an estimate of the duration of pregnancy with all these measures. On the other hand, it was demonstrated that the ratio foetal haemoglobin/weight was a considerably more accurate index of the duration of pregnancy. The scatter was here greatly reduced as compared with conventional methods, the precision in the estimate being almost twice as great. Accordingly this ratio was proposed as an index of the gestational age.

As was, however, pointed out in the above investigation, based on observations made on 61 newborn infants (Brody, 1958), further work on a larger material was thought necessary for a thorough evaluation of the proposed method. This has now been done and the present paper is a summary of some of the results.

The investigation also includes an analysis of the correlation between weight and post-menstrual age. It was deemed desirable to compare the accuracy and precision of the new method with those obtained with one of the most commonly employed conventional methods and, furthermore, to base this comparison on data from the same material.

Material and Methods

The material consists of 270 newborn infants. Except for prematurity in a certain number of cases, they were all healthy infants of sound mothers. In no case was iso-immunization found. All infants were delivered spontaneously without complications.

Fifteen subjects weighed less than 2,500 g. and 40 infants had a birth weight of more than 4,000 g. The total range was from 1,220 to 4,990 g. The youngest infant was born in the 29th week of pregnancy and the oldest in the 44th week.

The duration of pregnancy was calculated from the first day of the last menstrual period. Only cases where exact information on this point was available were included. These data were corroborated by information given as to the time when foetal movements were first felt. The material only comprises patients with apparently regular 28–30 day cycles during one year prior to pregnancy.

Blood from the umbilical cord was withdrawn within a few minutes after birth and before separation of the placenta. Extreme care was taken to avoid contamination with maternal blood. Sampling was performed in heparinized glass tubes. The proportions of foetal and adult haemoglobin were determined according to Betke (1951, 1954) as modified by Brody (1958). A Zeiss quartz spectrophotometer has been employed for all the determinations.

The weight data of the newborn infants were taken from the hospital records.

Statistical analysis of the material was performed according to Snedecor (1957) and Hald (1952). The standard error of the estimate was evaluated by calculation of the confidence limits for the value of x (=post-menstrual time) corresponding to an observed y-value (=weight, foetal haemoglobin or ratio foetal haemoglobin/weight). The P per cent confidence interval was calculated according to the formula

$$\bar{x}+\frac{y-\bar{y}}{\hat{b}} \pm \frac{t_p \cdot S}{\hat{b}} \sqrt{\left[\left(1+\frac{1}{n}\right)+\frac{y-\bar{y}}{\hat{b}S(x-\bar{x})^2}\right]}$$

where $\bar{x}$ and $\bar{y}$=the arithmetic means

t_p=the 100–P per cent value of the t-distribution

$$s=\sqrt{\frac{1-r^2}{n-2}\cdot S(y-\bar{y})^2}$$

$$r=\sqrt{\frac{[S(x-\bar{x})(y-\bar{y})]^2}{S(x-\bar{x})^2 \cdot S(y-\bar{y})^2}}$$

$$\hat{b}=b-\frac{t_p^2 \cdot S^2}{bS(x-\bar{x})^2}$$

$$b=\frac{S(x-\bar{x})(y-y)}{S(x-\bar{x})^2}$$

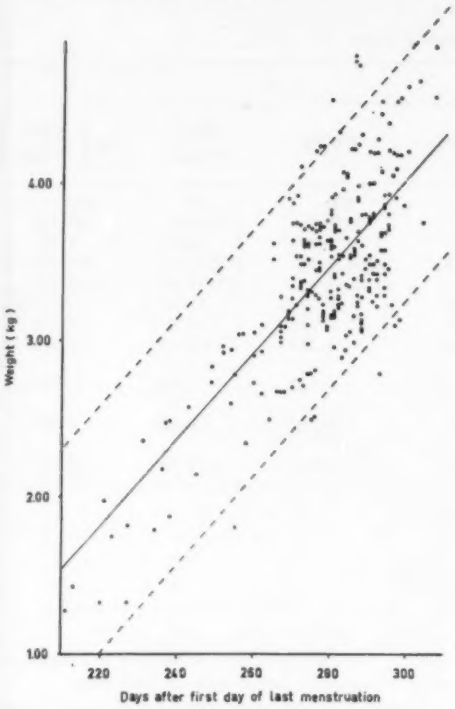

FIG. 1

Weight of newborn infants plotted against foetal age. Equation of regression line: $Y=0{\cdot}028x+0{\cdot}97$ (provisional scale: 90=280 days after first day of the last menstrual period).

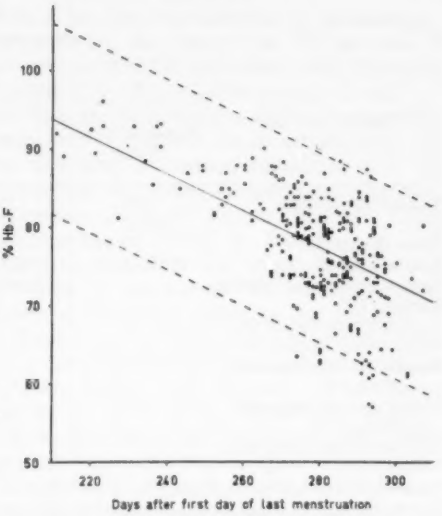

FIG. 2

Foetal haemoglobin expressed as a percentage of total haemoglobin plotted against foetal age. Equation of regression line: $Y=-0{\cdot}2285x+97{\cdot}97$ (provisional scale: 90=280 days after first day of the last menstrual period).

RESULTS

The relationship between weight and post-menstrual age is graphically demonstrated in Figure 1. The regression of weight on age has been calculated and the pertinent statistical data are summarized in Table I. The correlation is statistically highly significant ($P<0{\cdot}001$). Considerable biological variation is, however, noticed. This causes a large scatter around the regression line and influences, accordingly, the accuracy of this factor as an index of the duration of pregnancy. A quantitative expression for the precision of the method is the 95 per cent confidence interval expressed in units of the x-axis. For a y-value corresponding to the arithmetic mean ($=\bar{y}$) it amounts to $\pm 28{\cdot}0$ days and increases somewhat for other y-values according to the first statistical formula under Material and Methods.

Figure 2 is a scattergram of the relation between the proportion of foetal haemoglobin in the cord blood (expressed as a percentage of total haemoglobin) and post-menstrual age. The data from the statistical analysis of the correlation are found in Table I. A high statistical significance has been established ($P<0{\cdot}001$). An appreciable biological variation is, however, observed. The 95 per cent confidence interval in days for $y=\bar{y}$ is $\pm 53{\cdot}1$.

As the next step the relationship between the ratio foetal haemoglobin/weight and post-menstrual age was examined. The scattergram is shown in Figure 3. The correlation is highly significant (Table I). A considerable reduction in the variation is found. The scatter is markedly decreased and a remarkable increase in precision

TABLE I

Survey of Statistical Data

Statistical Term*	x	y			
	Post-menstrual Time†	Weight‡	Hb-F§	$\frac{\text{Hb-F}}{\text{Weight}}$	$\text{Log}\left[\frac{\text{Hb-F}}{\text{Weight}}\right]$
Number of variables ..	270	270	270	270	270
Sum	23755	926·00	21026·2	6504·9	368·177
Mean ($\bar{x}$ resp. $\bar{y}$)	87·98	3·43	77·87	24·09	1·36
Sum of squares	2166841	3282·6552	1651676·54	177212·73	505·773971
Sum of products of x and y		83660·23	1832358·9	537678·9	31938·012
Variance (S^2)		0·166	38·27	18·24	0·00384
Correlation coefficient (r) ..		0·764	−0·530	−0·873	−0·850
Regression coefficient (b) ..		0·0285	−0·2285	−0·451	−0·005918
Standard error of regression coefficient		0·00147	0·022	0·015	0·00022
Significance of regression coefficient (P)		<0·001	<0·001	<0·001	<0·001
95% confidence interval in days ($y=\bar{y}$)		±28·03	±53·09	±18·54	±20·50

* For further explanations see under Material and Methods.

† Time in days.

‡ Weight in kg.

§ Hb-F=foetal haemoglobin in per cent of total haemoglobin.

and accuracy is obtained by employing this ratio as an index of the duration of pregnancy. With this method an estimate of the duration of pregnancy is possible with a 95 per cent confidence interval of ±18·5 days ($y=\bar{y}$).

Finally, the logarithms of these ratios have been plotted against the post-menstrual age (Fig. 4). Statistical analysis reveals a 95 per cent confidence interval of ±20·5 days ($y=\bar{y}$).

DISCUSSION

The various factors investigated in this study have been correlated to the post-menstrual duration of pregnancy. In an analysis of the precision and accuracy obtainable by employing these factors as criteria of the duration of pregnancy it is necessary to examine the error inherent in the appraisal of the gestational age from the menstrual history.

It is well known that the duration of pregnancy as judged from the last menstrual period exhibits very large variations. The average duration is 281·7 days (Schildbach, 1953), but Stewart (1952), for example, has observed a pregnancy with a post-menstrual age of 349 days.

One factor causing these variations is intentional deception on the part of the patient in the information given on her last menstrual period. A more frequent error, however, is introduced unintentionally. Many patients are unable to recall the exact menstrual data prior to pregnancy. The existence of this error in material with reported precise data has been satisfactorily demonstrated with statistical methods by Frazier (1959).

A second factor is the variable interval between menstruation and ovulation. Corner, Farris and Corner (1950) have investigated this problem with histological as well as endocrinological methods. They found that ovulation occurs from day 8 to day 20 of the cycle. In the majority of cases it was noted between days 11 and 14, with a peak on day 13. Riley, Dontas and Gill (1955) used somewhat different criteria for the time of ovulation. Their study was based on serial vaginal smears as well as basal temperature curves. In a large series of patients com-

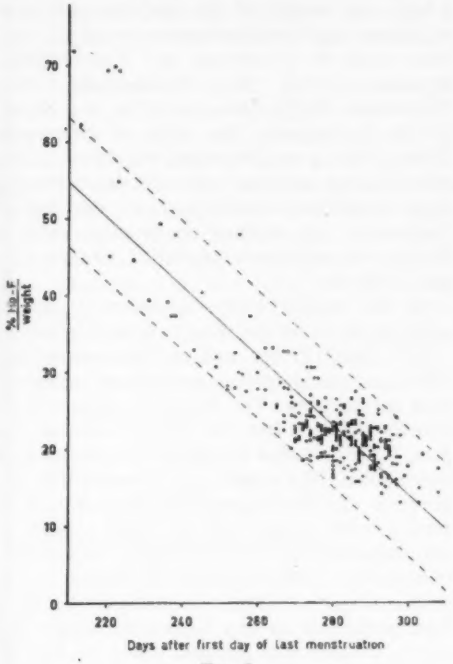

FIG. 3

Ratio foetal haemoglobin/weight plotted against foetal age. Equation of regression line: $Y=-0{\cdot}451x+63{\cdot}77$ (provisional scale: 90–280 days after first day of the last menstrual period).

prising 126 subjects they were able to demonstrate a relationship between the day of ovulation and the length of the cycle. Their data indicate that two-thirds of all patients with 28-day cycles may be expected to ovulate between days 12 and 16 of the cycle. The standard error of estimate was $\pm 1{\cdot}89$ days, corresponding to a 95 per cent confidence interval of $\pm 3{\cdot}78$ days.

An illustration of the variability of the duration between the last menstrual period and ovulation is also afforded by studies on the time of conception in relation to the menstrual cycle. Conception is here used in the sense of intercourse leading to pregnancy. An impressive body of data has been collected by Hollenweger-Mayr (1950). She reports on 903 patients of her own and 2,790 cases from the literature. Frequency analysis exhibits a peak on day 8 of the cycle, but demonstrates also that conception is possible throughout the menstrual cycle. As the time-interval between conception and impregnation, i.e., fusion of sperm and egg cells, is considered to be shorter than 48 hours (Belonoschkin, 1939), it remains an unexplained fact that the peak incidence of ovulation in relation to the menstrual cycle occurs several days earlier in the material of Hollenweger-Mayr (1950) than is inferred from other investigations on the time of ovulation (Corner, Farris and Corner, 1950; Riley, Dontas and Gill, 1955). One possible explanation is that psychological factors may cause premature as well as paracyclical ovulations in the material of Hollenweger-Mayr (1950), based on single intercourses between couples separated from each other for long periods.

A factor of considerable importance in connexion with the present investigation is the variation in the duration of pregnancy *per se*. As is evident from the above, we must take into account an error in the menstrual dating and a variability in the time of ovulation. But it should also be emphasized that the time of gestation as defined from the moment of impregnation is not a fixed period, but subject to considerable individual variations.

This problem has been approached in various ways. Hollenweger-Mayr (1950) determined the time from conception to delivery and found a mean of 272·3 days. Assuming a Gaussian distribution for the duration of pregnancy as calculated from the time of conception, Hollenweger-Mayr analyzed her material statistically, after dividing it into groups according to length of the newborn from 48 to 54 cm. As might be expected, there was a relationship between length and average gestation time. The standard error of estimate, on the other hand, showed very small variations. The mean for all groups was $\pm 9{\cdot}5$ days.

Hollenweger-Mayr's analyses (1950) have been criticized by Schildbach (1953). By refined statistical methods he was able to demonstrate that the distribution of her material did not fit

the Gaussian distribution curve. He calculated the skewness* and kurtosis* of her material based on data relating to conception, and found that they far exceeded their respective errors, as compared with these ratios for an empirical curve fitting the Gaussian distribution. At the same time, however, Schildbach (1953) was able to demonstrate that the variation in the duration of pregnancy did actually approximate to the Gaussian curve when correct data on its commencement were used. He based his calculations on the material of Stewart (1952). Proceeding from basal temperature records during the month of conception this author was able to determine the time of ovulation to within a few days. His investigation seems to be the most important contribution to our present knowledge on individual variations in gestation time for mature infants. The average post-ovulatory duration in 135 cases was 267·7 days. For this material Schildbach (1953) found a distribution with skewness and kurtosis well within the respective errors, thus fitting the normal distribution curve. The standard error of estimate was ±7·31 days. This implies that the 95 per cent confidence interval for the duration of pregnancy *per se* is ±14·62 days.

Summarizing the above remarks, it may be said that the variability of the post-menstrual duration of pregnancy is influenced by at least three factors: (1) the reliability of the date of the last menstrual period, (2) the variation in the time incidence of ovulation, (3) the variation in the duration of pregnancy *per se* (impregnation to delivery). The factors under 2 and 3 are beyond control in this material. The exclusive incorporation in this material of cases with regular menstrual data for a year prior to pregnancy and of patients with 28–30 day cycles, who gave apparently reliable information as to the date of the last menstruation and the time for the first foetal movements, was intended to reduce this error as much as possible.

An extensive literature exists on the relationship between such morphological data as the length and weight of the newborn and post-menstrual age. Contributions to the subject have been made by Guthmann and Knöss (1939), Hosemann (1948, 1949), Freudenberg (1950), Wichmann (1950), Etterich (1953) and Brody (1958). Particularly the work of Hosemann (1948, 1949) is a systematical evaluation of the precision and accuracy obtainable by employing these parameters as criteria of the duration of pregnancy. An estimate is possible with a 95 per cent confidence interval of between ±33 and ±36 days.

In the present study the accuracy in the estimate based on the weight of the newborn is ±28·0 days (95 per cent confidence interval). This means an increase in precision as compared with earlier work. The reason is apparently to seek in the fact that the present material has been rigidly selected as regards menstrual data (see above). The result may illustrate the importance of collecting material large enough to yield reliable results and yet small enough to permit personal and critical enquiry on key data in connexion with pregnancy. In contrast to this practice most investigations on the subject have been performed on very large series comprising several thousands of patients, where the decisive information on the date of the last menstruation has been obtained only by retrospective examination of the case histories. The degree of reliability of such information is thus beyond control.

For a review of the literature on the relationship between the proportion of foetal haemoglobin and the degree of development of the newborn infant either in terms of post-menstrual age or weight the reader is referred to Brody (1960). There is almost unanimous agreement on such a relationship.

The correlation between foetal haemoglobin and the duration of pregnancy has been studied earlier (Brody, 1958). A 95 per cent confidence interval of ±33·7 days was found. The corresponding figure in the present material is ±53·1 days. The main reason for this discrepancy seems to reside in the fact that in the first analysis (Brody, 1958) values before day 250 were excluded. In this study all values from day 205 have been analyzed to yield an overall estimate. The conclusion must be that the

* Skewness=asymmetry; Kurtosis=curvature (Mainland, D., *Elementary Medical Statistics*, 1952. Saunders, Philadelphia).

proportion of foetal haemoglobin cannot *per se* be used as an accurate index of the duration of pregnancy.

A remarkable increase in accuracy and precision is obtained by relating the ratio foetal haemoglobin/weight to the post-menstrual gestation time (Fig. 3). From Table I it is apparent that the scatter is considerably reduced. The 95 per cent confidence interval is $\pm 18 \cdot 5$ days. The correlation between the logarithms of these ratios and the duration of pregnancy has also been analyzed. This was done because of the finding in an earlier study (Brody, 1958) that this logarithmic transformation seemed somewhat further to reduce the scatter. In the present larger series, however, this is not the case. As is indicated in Figure 4, this may be due to a curvilinear regression of the variables.

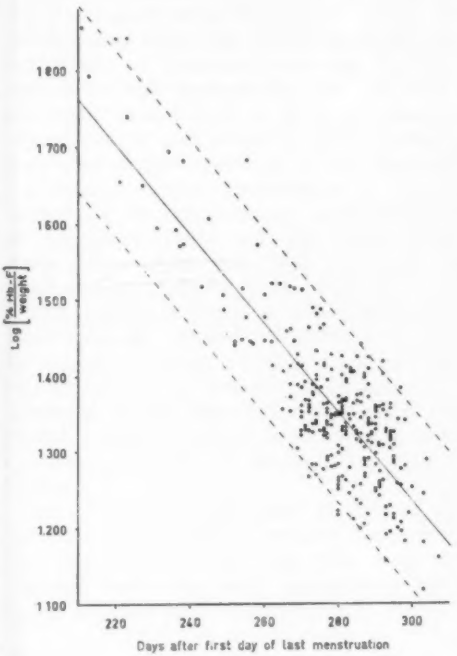

FIG. 4

Logarithm of ratio foetal haemoglobin/weight plotted against foetal age. Equation of regression line: $Y = -0 \cdot 005918x + 1 \cdot 885$ (provisional scale: 90=280 days after first day of the last menstrual period).

From the above results it is evident that the ratio foetal haemoglobin/weight seems to be the most accurate estimate of the duration of pregnancy. This index apparently provides a method affording a precision approximately double that obtained with present conventional methods.

Inevitable variation in the method based on the menstrual history derives from the scatter in ovulation (95 per cent confidence interval $= \pm 3 \cdot 78$ days) (Riley, Dontas and Gill, 1955), individual variation of the proper gestation time (95 per cent confidence interval $= \pm 14 \cdot 62$ days) (Schildbach, 1953) and variation due to inexact dating of the last menstrual period. Accurate information on the magnitude of the error introduced by this last factor is, however, difficult to obtain. The computation of available data suggests that the theoretical limits of precision for a method elaborated with given biological premises have been reached.

The correlation between the ratio foetal haemoglobin/weight points to certain rigidly controlled relations between foetal and adult haemoglobin and weight. The results provoke speculation on the regulation of the foetal and adult haemoglobin mass during development and their correlation to foetal weight. This problem has already been tackled.

SUMMARY

The accuracy and precision of a new method for the determination of the duration of pregnancy based on the ratio foetal haemoglobin/weight have been studied. Concomitantly the correlation between the factors of foetal haemoglobin and weight versus the duration of pregnancy has been analyzed.

The method permits an estimate with a 95 per cent confidence interval of $\pm 18 \cdot 5$ days, which is a considerable improvement on existing conventional methods.

Consideration of various errors inherent in the method of age determination based on the last menstrual period indicates that the precision of the new method approaches the theoretical limits with given biological premises.

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FOETAL AND ADULT HAEMOGLOBIN MASS IN RELATION TO FOETAL DEVELOPMENT

BY

SAM BRODY

AND

BO A. NILSSON

Department of Women's Diseases, Karolinska Sjukhuset, Stockholm and King Gustcf V Research Institute, Stockholm, Sweden

INTEREST in the different types of haemoglobin, foetal and adult, in the blood of the foetus and the newborn infant has increased during the last decade. A relationship between the proportion of foetal haemoglobin in the cord blood and foetal development in terms of duration of pregnancy or birth weight has been repeatedly demonstrated (for references to the literature see Brody, 1960a). Furthermore a precise method for the determination of the duration of pregnancy based on the ratio foetal haemoglobin/weight has been advanced in previous papers (Brody, 1958, 1960b).

This correlation brings us to the problem of the relationship between the foetal and adult haemoglobin fractions and foetal development, i.e., whether the two first-mentioned factors are correlated to this latter factor or whether the altered proportion during intra-uterine growth is due only to a gradual change in one of these fractions.

The study was undertaken as part of an investigation intended to elucidate these problems. An approach has here been made by assessing foetal and adult haemoglobin mass during the later parts of pregnancy.

MATERIALS AND METHODS

The subjects of this investigation were 14 newborn infants weighing from 2,420 to 4,100 g. The infants were born of healthy women attending the obstetric clinic of this medical centre and with uncomplicated pregnancies and deliveries.

Delayed umbilical cord ligation was practised in each case, i.e., the cord was tied after pulsations had ceased. Blood volume determinations were carried out between 3 and 10 hours after birth.

Plasma volume determinations were performed with the use of the dye Evans blue (T-1824). With careful aseptic precautions the umbilical cord was divided approximately 2 cm. from the abdominal wall. A sterilized polythene catheter was introduced into the umbilical vein. After withdrawal of a few ml. of blood a sample of approximately 7 to 8 ml. was collected. Exactly 5 ml. of a 0·02 per cent Evans blue solution in physiological saline was injected with a syringe *ad modum* Wiklander (1956) and the catheter was washed with blood. After 7 to 8 minutes a new catheter was inserted and after exactly 10 minutes a new blood sample was withdrawn. The cord was now tied and dressed. No untoward sequelae were noticed.

The concentration of the dye was measured with a Zeiss spectrophotometer in 1 cm. cells and with pre-injection plasma as a blank. The degree of haemolysis was determined from the ratio of the absorbency at 620 mμ to that at 578 mμ (von Porat, 1951). Only one sample had to be discarded because of haemolysis.

Standards were prepared by adding Evans blue dye solution to the blank sample. Sample

TABLE I

Case	Post-menstrual Age	Weight (kg.)	Haemoglobin (g./100 ml.)	Foetal Haemoglobin (% of Total Haemoglobin)	Haematocrit* (%)
1	297	3·93	19·18	60·2	64·7
2	279	3·44	16·62	80·3	52·9
3	272	2·99	21·13	80·0	60·8
4	294	4·10	17·81	69·7	56·8
5	283	3·74	17·85	74·3	54·9
6	287	2·79	21·44	76·1	68·6
7	235	2·42	16·74	89·5	53·9
8	303	3·99	15·31	68·0	51·9
9	268	3·31	20·89	82·3	66·6
10	280	3·83	17·57	76·1	56·8
11	270	3·12	17·57	81·6	56·4
12	293	3·59	16·81	71·5	53·9
13	258	3·00	19·89	83·2	55·9
14	283	3·20	18·23	78·5	54·9

* Corrected for trapped plasma (see Material and Methods).

as well as dye solution was measured by weight, since volumetric determinations seemed to entail an appreciable scatter in standard values. The reason for this resides probably in the fact that the Evans blue solution adheres to the walls of the capillary pipette (Mollison, Veall and Cutbush, 1950). With the gravimetric technique the difference between various standard samples did not exceed 2 to 3 per cent. Linearity between dye concentration and absorbency was noticed in the range of concentration found in the present material.

Haemoglobin concentration was measured as described in detail earlier (Brody, 1960a).

The haematocrit value was determined with an International Hemacrit centrifuge at 11·000 r.p.m. for 4 minutes. Trapped plasma was compensated for by multiplying all observed readings by the factor 0·98 (Estborn, personal communication). These corrected readings were then multiplied by the factor 0·87 to obtain the true proportion of cells in unit volume of blood in the body as a whole (body/venous haematocrit=0·87, Mollison, Veall and Cutbush, 1950).

The proportions of foetal and adult haemoglobin were calculated by measuring the rate of alkali denaturation according to the method of Betke (1951, 1954) as modified by Brody (1958).

Statistical analysis was performed according to conventional statistical methods (Snedecor, 1957).*

RESULTS

Basic data such as post-menstrual age at birth, weight, haemoglobin concentration, proportion of foetal haemoglobin and haematocrit are summarized in Table I.

Table II gives the individual data on total plasma and blood volumes as well as these factors related to body weight. The average plasma volume per kg. body weight was 47·27 ml. with a standard deviation of ±9·24. The range was from 31·17 to 60·55 ml. per kg. The values for blood volume ranged from 76·96 to 115·55 ml. per kg. The mean was 94·74 ml. with a standard deviation of ±12·29.

The total haemoglobin mass varied from 43·81 to 77·14 g. with a mean value of 58·38 and a standard deviation of ±9·82 (Table III). The mean per kg. body weight was 17·29 g. with a standard deviation of ±2·08. Foetal haemoglobin mass ranged from 35·04 to 57·32 g. with a mean of 44·35 g. and a standard deviation of ±6·82.

* The duration of pregnancy was calculated from the first day of the last menstrual period.

TABLE II

Case	Plasma Volume Total (ml.)	Plasma Volume (ml./kg.)	Blood Volume Total (ml.)	Blood Volume (ml./kg.)
1	144·16	36·68	328·38	83·56
2	170·37	49·53	314·92	91·55
3	111·83	37·40	255·90	85·59
4	178·19	43·46	351·46	85·72
5	226·45	60·55	432·16	115·55
6	86·96	31·17	214·72	76·96
7	139·36	57·59	261·71	108·14
8	209·03	52·39	380·40	95·34
9	138·29	41·78	327·70	99·00
10	184·23	48·10	363·37	94·87
11	137·24	43·99	270·69	86·76
12	213·13	59·37	400·24	111·49
13	127·28	42·43	246·91	82·30
14	183·61	57·38	350·40	109·50
Mean		47·27		94·74
S.D.		±9·24		±12·29

S.D. is standard deviation.

TABLE III

Case	Haemoglobin Mass Total (g.)	Haemoglobin Mass (g./kg.)	Foetal Haemoglobin Mass Total (g.)	Adult Haemoglobin Mass Total (g.)
1	62·98	16·03	37·91	25·07
2	52·34	15·22	42·03	10·31
3	54·07	18·08	43·26	10·81
4	62·60	15·27	43·63	18·97
5	77·14	20·63	57·32	19·82
6	46·04	16·50	35·04	11·00
7	43·81	18·10	39·21	4·60
8	58·24	14·60	39·60	18·64
9	68·46	20·68	56·34	12·12
10	63·84	16·67	48·58	15·26
11	47·56	15·24	38·81	8·75
12	67·28	18·74	48·11	19·17
13	49·11	16·37	40·86	8·25
14	63·88	19·96	50·15	13·73
Mean	58·38	17·29	44·35	14·04
S.D.	±9·82	±2·08	±6·82	±5·66

S.D. is standard deviation.

TABLE IV

Statistical Term	Regression					
	Hb on Weight	Hb on Time	Hb-F on Weight	Hb-F on Time	Hb-A on Weight	Hb-A on Time
Correlation coefficient (r)	0·683	0·499	0·271	0·267	0·865	0·834
Regression coefficient (b)	13·50	0·278	3·701	0·103	9·803	0·267
Standard error of regression coefficient ..	4·12	0·14	3·79	0·108	1·64	0·051
Standard deviation from regression line (s) ..	7·44	8·86	6·83	6·84	2·95	3·26
Statistical significance of correlation (P)	0·001<P<0·01	0·05<P<0·1	>0·2	>0·2	<0·001	<0·001

Hb=total haemoglobin mass; Hb-F=foetal haemoglobin mass; Hb-A=adult haemoglobin mass; time=post-menstrual day of birth.

Adult haemoglobin mass varied considerably more. The smallest value encountered in this series was 4·60 g. and the largest was 25·07 g. The mean was 14·04 g. and the standard deviation ±5·66.

The correlations between total, foetal and adult haemoglobin mass and post-menstrual age at birth and birth weight have been analyzed. The results are summarized in Table IV. As is apparent there is a highly significant correlation between adult haemoglobin mass and foetal maturity in terms of intra-uterine age or weight. On the other hand no such correlation was observed between foetal haemoglobin mass and the indices employed for foetal maturity. The analysis also indicates a correlation between total haemoglobin mass and foetal maturity.

DISCUSSION

The results of the present investigation of plasma and blood volumes as well as total circulating haemoglobin mass are in good agreement with earlier findings (Mollison, Veall and Cutbush, 1950; Stahlman, Karlberg and Lind, 1951; Sisson, Lund, Whalen and Telek, 1959). Not previously reported, to the best of our knowledge, are values on circulating foetal and adult haemoglobin mass.

The considerable standard deviation for adult haemoglobin mass (Table III) indicates an appreciable individual variation and possibly also that the values do not fit a normal distribution curve.

Statistical analysis reveals good correlation between adult haemoglobin mass and foetal development ($P<0·001$). No such correlation was found for foetal haemoglobin mass. The statistical analysis also suggests a correlation between total haemoglobin mass and foetal maturity. Obviously this correlation is caused by the variation of the adult haemoglobin component.

The present series indicates that a gradual increase in adult haemoglobin mass causes the change in proportion of foetal and adult haemoglobin during intra-uterine growth. The increase in circulating adult haemoglobin mass was anticipated but the results on foetal haemoglobin mass were somewhat unexpected. This latter fraction thus seems to be constant during the time period studied within limits of error due to individual and experimental variation. This indicates a delicately balanced regulating mechanism operating throughout the later part of pregnancy. We are now in the process of investigating from which stage of intra-uterine development this mechanism is functioning and, furthermore, the effect of certain pathological states such as erythroblastosis foetalis on the different haemoglobin fractions.

Summary

Circulating foetal and adult haemoglobin mass have been determined in newborn infants of varying intra-uterine age in an attempt to ascertain which of these fractions is correlated with the foetal maturation process. In the time period studied (from day 235 to day 303) the foetal haemoglobin mass is apparently constant per individual within limits of biological and experimental variation. Adult haemoglobin mass, on the other hand, shows a highly significant correlation with foetal development. The change in the proportions of foetal and adult haemoglobin during this phase of pregnancy is thus solely due to a gradual increase in the adult haemoglobin mass.

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SOME ASPECTS OF CYTODIAGNOSIS OF CANCER OF THE CERVIX, WITH SPECIAL REFERENCE TO THE "PICK-UP RATE"*

BY

AGNES L. SCOTT, M.B., M.R.C.P.(Ed.), D.P.H.
Consultant Pathologist
Royal Infirmary, Dumfries

THE conception that the exfoliated or abraded cell can indicate the changes that are occurring in the tissue of its origin is revolutionary and contrary to the traditional pathological philosophy as stated in 1904 by Dürck: "The shape of the cell alone must never be taken as a criterion by which to judge the genesis of a tumour. Hence there is no such thing as a 'carcinoma cell' or a 'sarcoma cell'; the type of tumour, whether it be epithelial, connective tissue, or mixed, can be determined positively only by the arrangement of the cells with regard to one another." There is a natural reluctance to place emphasis on single cell appearance and, for many, the dictum that "microscopic diagnosis of cancer is mainly a tissue pattern and not from single cells" still holds.

The pioneer work in cytological diagnosis of cancer of the uterus was instigated by Papanicolaou in 1928 and five years later he published a brief paper on the practical usefulness of the vaginal smear which was received with scant interest, other than as a subject for research as opposed to clinical use. In 1939, in association with Traut and Marchetti, the early work was repeated and the results (Papanicolaou and Traut, 1943), aroused the interest of clinicians. Since then there has been a flood of literature by authorities of differing degree expressing opinions varying from utmost enthusiasm to guarded approval, the latter, needless to say, to be found in publications emanating from Great Britain.

It is my opinion, shared by others in this country, that, in experienced hands, cytological methods can provide a valuable means of picking up cases of unsuspected carcinoma at a time in the patient's history when clinical evidence is as yet undeveloped. This is seen by the trend in the more recent publications to concentrate on the "pick-up rate", which is frequently used as a justification for a time-consuming procedure, for which special training is required.

However, from a survey of the literature there appears to be a wide divergence of opinion as to what constitutes a true "pick-up". The "pick-up rate" of so-called non-suspect cases ranges, for example, from as low as 2 per 1,000, as stated by Langley (1959) of Manchester, to as high as 15/1,000 in south-east Scotland (College of General Practitioners, 1958).

TABLE I
Pick-up Rates

Per 1,000	
2·0	Manchester (Langley)
3·5	Birmingham (McLaren)
4·0	San Diego, California (Martin *et al.*)
4·3	University of Tennessee (Erickson *et al.*)
4·6	Dumfries (Scott)
6·0	Rhode Island, New York (Song *et al.*)
7·0	Detroit, Michigan (Siddall)
9·0	Mayo Clinic, Rochester (Dahlin *et al.*)
10·0	Edinburgh (Anderson)
12·0	Newcastle (Way)
15·0	Edinburgh (G.P. Survey)

* Based on an address presented to the Edinburgh Obstetrical Society on 13th January, 1960.

The purpose of this communication is to put forward a simple and realistic basis upon which the "pick-up rate" can be assessed, as this is a matter of some moment in justifying the value of cytological methods. It is suggested that this rate be described in two terms:

(I) General Pick-up Rate, and

(II) Absolute Pick-up Rate.

(I) The *General Pick-up Rate* is calculated from:

(*a*) All cases where a local lesion of the cervix is visible, considered "non-malignant" on clinical examination and in which a positive smear was subsequently substantiated by histological malignancy; or

(*b*) In which there is a suspicious history, such as post-menopausal or post-coital bleeding and an apparently healthy cervix; and

(*c*) Those cases free from macroscopic pathology or suspect symptoms and yet had a positive smear and histological confirmation of malignancy.

(II) The *Absolute Pick-up Rate* comprises the cases in group (*c*).

This dichotomy is justified in as much as one criticism of the cytological service has been that a significant number of pick-ups would have been found from the clinical history or local findings and where such findings merited biopsy *de novo*. This may well be a valid criticism but the truly significant value of a cytological service arises from the case, above clinical suspicion, which comes to biopsy as a result of a smear which has produced an unanticipated and unsuspected positive. That there exists such an absolute pick-up rate must be considered adequate justification for routine cytology in present-day gynaecological practice and this must entail, in that it is routine, the obtaining of a smear from each and every woman who attends a gynaecological out-patient department for whatever reason.

The wide variation in the "pick-up rate" as evidenced in Table I must arise from the differing degrees of interpretation of a "pick-up". Comments of a similar nature have been made by others. McLaren and others (1956) state in relation to their own findings "there is no clear definition of the term 'pick-up'" and so "valid comparisons between this and various other studies cannot be made" and Langley (1959) comments on the present "subjective" nature of a pick-up. Anderson (1959) in his recent paper on "The Management of the Cytology Test" defines the unsuspected positive smear as one which "comes from a cervix which a clinician regards as showing no obvious cancer when he sees it with the aid of a speculum" and makes a plea that "the definition must be kept simple".

TABLE II

Dumfries and Galloway, 1955–1959

Smears	5,072
General pick-ups	23
Absolute pick-ups	6
General pick-up rate	4·6/1,000
Absolute pick-up rate	1·2/1,000

In that the female genital tract offers unique advantage of accessibility to a notoriously high cancer incidence organ, the uterus, and in particular, the cervix, correlation between clinical and cytohistological findings can readily be effected in a manner which is not possible in other systems of the body where cytology may be of value, for example, the respiratory, alimentary and urinary tracts. In view of this advantageous location of the uterine cervix, the major research and clinical application of cytological methods have been concentrated there, and while a high degree of uniformity has been attained in method and cytological and histological assessment, there is a great lack of correlation between the clinical and cytohistological findings. This has resulted in a loose determination of the pick-up rate of malignant disease and the variation in statistics arrived thereby may well denigrate the true value of cytological procedure.

ILLUSTRATIVE CASES

Case 1. (Absolute Pick-up.)

Mrs. S.F. (Reg. No. 48784). Age 37 years. Para-1 (child aged 15).

Patient was admitted to hospital in July, 1958, with a diagnosis of acute left-sided pyosalpinx for which she received a course of Crystomycin. She was seen at a gynaecological clinic on 25th August, 1958, when she

complained of a little residual pain in the left iliac fossa with some leucorrhoea. On examination, there was tenderness in the left iliac fossa with thickening of both parametria.

The cervix appeared healthy and routine smears were taken.

Carcinoma cells were present in the smear (Fig. 1) and patient was admitted for ring biopsy and curettage.

Histological examination of the biopsy of cervix showed an active intra-epithelial carcinoma (Fig. 5) arising in the endocervix.

Total hysterectomy with left salpingo-oöphorectomy was carried out on 9th September, 1958 (the right ovary had been removed on some previous occasion). The patient has remained well since.

Case 2. (Absolute Pick-up.)

Mrs. H.R. (Reg. No. 500). Age 36 years. Para-5 (last child aged 5).

Seen at a gynaecological clinic on 17th October, 1958, with a complaint of stress incontinence. Arrangements were made for cystogram; further action (? sling or other operation) depending on the results of the cystogram.

The cervix appeared healthy and routine smears were taken.

Carcinoma cells were present in the smear (Fig. 2) and patient was admitted for ring biopsy and curettage.

Histological examination of the biopsy of cervix showed an intra-epithelial carcinoma of the cervix (Fig. 6) arising in the endocervix.

Total hysterectomy with left salpingo-oöphorectomy was carried out on 25th November, 1958. No residual malignant tissue remained in the uterus.

Case 3. (General Pick-up.)

Mrs. E.D. (Reg. No. 123520). Age 34 years. Para-3 (last child aged 6).

Patient was referred to a gynaecological clinic on 27th January, 1958, because of polymenorrhoea.

The cervix showed mild chronic infection and routine smears were taken.

Carcinoma cells were present in the smear (Fig. 3) and patient was admitted for ring biopsy and curettage. Histological examination of the biopsy of cervix showed an infiltrating squamous carcinoma (Fig. 7).

Wertheim hysterectomy was performed on 4th March, 1958.

Infiltrating carcinoma was confirmed in the cervix. There was no evidence of lymph gland involvement. The patient has remained well.

Case 4. (General Pick-up.)

Mrs. A.H. (Reg. No. 108683). Age 44 years. Para-5 (last child aged 11).

Referred to a gynaecological clinic on 15th May, 1956, with a diagnosis of anaemia and menorrhagia.

The cervix showed infection and polyposis and routine smears were taken.

Carcinoma cells were present in the smear (Fig. 4) and patient was admitted for ring biopsy and curettage.

Histological examination of the biopsy of cervix revealed an *in situ* cancer involving the glandular portion of the cervix (Figs. 8 and 9). Panhysterectomy was carried out on 14th June, 1956, and the patient remains well three years later.

Those who question the merits of a cytological service usually ask, "How many cases of unsuspected cancer of the cervix do you pick up in the course of a year and what percentage of the total patients screened does this represent?"

It thus becomes apparent that the questioner has to some degree established in his mind a general and absolute pick-up rate and is unconsciously evaluating the merits of the service on the latter, since any patient who attends a gynaecological clinic where routine screening is carried out may or may not present clinical features, by history or local findings, which merit histological investigation forthwith. From this it follows that under normal circumstances and where the cytological service is not in force, a residuum of patients would be dismissed from clinical supervision because the *ab initio* findings did not merit further investigation. It is from this group of patients that the absolute pick-up rate is obtained and from which critics would assess the merits of cytological procedure.

In the case of the selective employer of the cytological service the pick-up rate may well be misleading, since he tends to select cases already with suspicion. A high rate inevitably results over a small series when extended statistically to the order of a thousand or more. By contrast, where a routine service is used the pick-up rate will be correspondingly lower and more realistic.

Carcinoma *in situ* is a histological entity but patients who are found to have this condition may have a variety of concurrent symptoms—for example, backache, aberrations of the menstrual cycle or leucorrhoea, which may cause the patient to seek advice and the cervix may show local lesions such as an erosion or polyposis. But it is impossible to correlate these signs and symptoms with the histological picture of intra-epithelial carcinoma and it is highly improbable that they are directly related. Carter (1956) and his associates have pointed out that, in 275 patients with intra-epithelial carcinoma, 88·5 per cent were considered benign prior to smear and biopsy.

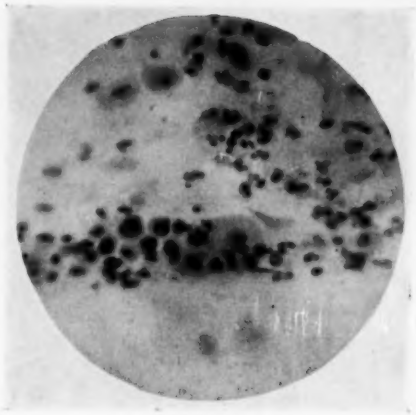

FIG. 1

A group of pleomorphic malignant cells, with a parabasal cell and a number of inflammatory cells, is seen in the lower field. ×250.

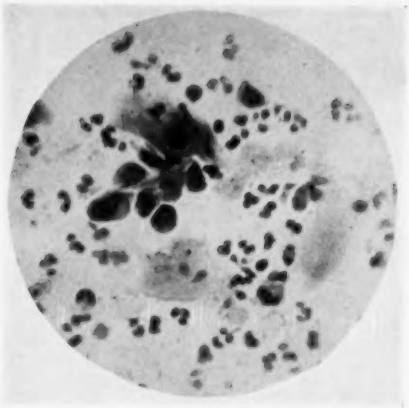

FIG. 2

The group of malignant cells, with an adjacent dyskariotic squame, shows pleomorphism, hyperchromatism and increased nucleo-cytoplasmic ratio. ×250.

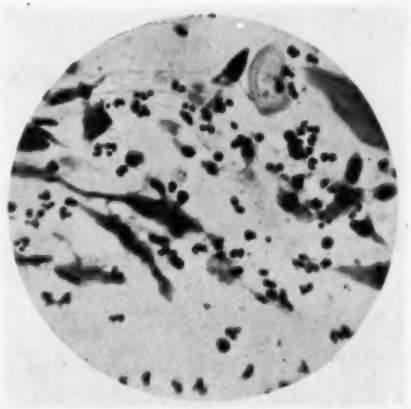

FIG. 3

"Fibre cells" are seen on the extreme left of the picture and undifferentiated malignant cells are present on the right. ×250.

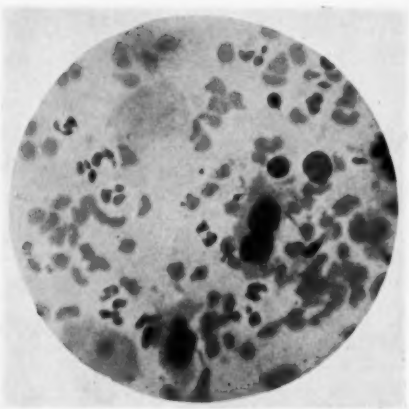

FIG. 4

The malignant cells, which are from the endocervix, show clumping of chromatin and some have lost their cytoplasm. ×250.

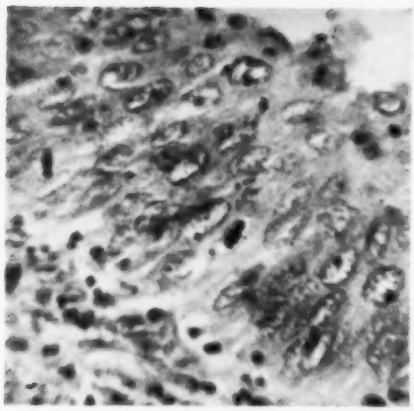

FIG. 5

Carcinoma *in situ*. The elongated cells show crowding and a parallel arrangement with no differentiation. Chromatin is distributed in coarse clumps and nucleoli are prominent in a number of the cells, many of which are in mitosis. ×250.

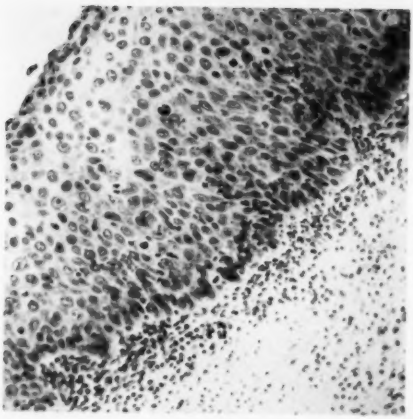

FIG. 6

Carcinoma *in situ*. There is pleomorphism, disarray and crowding of the cells. Nucleoli are prominent in a number. Mitotic figures are numerous. ×63.

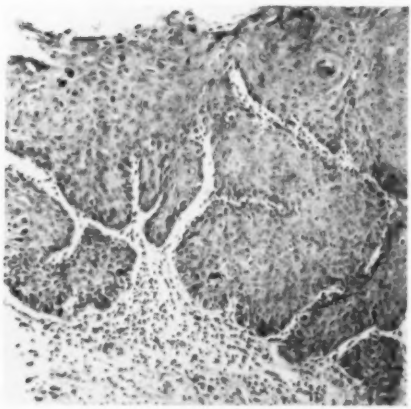

FIG. 7

Invasive squamous carcinoma. ×63.

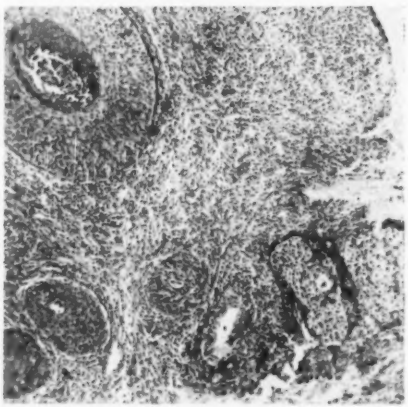

FIG. 8

Carcinoma *in situ* involving endocervical glands. The columnar epithelium is replaced by malignant tissue. ×63.

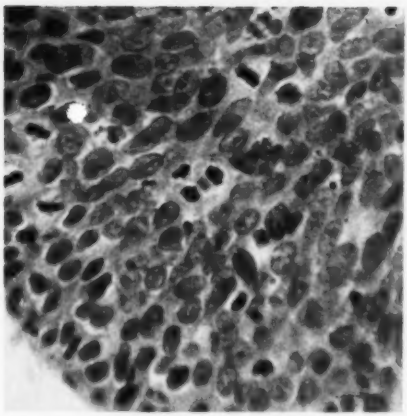

FIG. 9

Carcinoma *in situ*. High power view of part of the large gland seen in Figure 3. Pleomorphism and hyperchromatism are features of the nuclei and many of the cells are in mitosis. ×250.

Routine cytology is therefore a procedure apart from clinical experience and assessment of the individual case, but the latter is of value in attempting to reach a true pick-up rate.

Technical Aspects

The Smear

It is my experience that the majority of cervical carcinomas arise in the glandular portion, from the reserve cells, and are epidermoid in type, while much less frequently does the neoplasm arise primarily in the portio. This has been commented on by Marsh (1956): "Epidermal carcinoma of the cervix arises most frequently in the endocervical epithelium" and also by Clarke and Gilmore (1956) who state "Endocervical curettage is more efficient than biopsy of the portio". The most careful inspection, colposcopy, and the Schiller test may not detect an endocervical lesion and it is in such cases that cytological examination provides the superior diagnostic test.

The predilection for the initial site of carcinoma being the endocervix makes it necessary for the cervical smear to be adequate to include a sample of the cells from the endocervix. It is apposite to repeat the statement of Mussey and Soule (1959) that "the accuracy of the pathologist is in part proportional to the quality of the slide received". Immediate fixation to maintain cell structure is desirable although Oppenheim and his associates (1956) claim satisfactory results with the dried smear.

The Biopsy

I would at this point emphasize the importance and necessity of adequate ring biopsy, to include the squamo-columnar junction, which in effect is comparable with the conization technique of American practice. Segmental or other haphazard selection of material from the cervix is both inadequate and dangerous.

If the pathologist in the final issue has to decide the presence or absence of a lesion and its invasive or pre-invasive character, it is right to expect a biopsy (ring or conization) which includes the external os and lower portion of the cervical canal and also ideally curettings from the upper part of the canal. On occasion serial sectioning of the biopsy specimen may be necessary where there is an apparent discrepancy between the suspicious or positive smear and, at first sight, benign biopsy. To summarize the importance of technique in the smear and biopsy, reference is made to the opinion of Nieburgs (1956) that "statistical data of cervical carcinoma diagnosed by cytological methods depend not only on racial, social and other factors, . . . but also on techniques employed".

The obtaining of a smear need add no significant time to clinical investigation if a speculum examination is, as it should be, part of the routine examination. In the pathological department, the services of a technician trained and experienced in cytological procedure should be available and such a technician is competent to carry out the initial screening of smears. The final interpretation of the suspicious and positive smears must be the responsibility of the cytohistologist. Where a routine cytological service is in force, there will be an inevitable increase of material for histological examination but this should not be an insuperable problem for the department concerned.

It will thus be seen that variation in the pick-up rate may result from artificial loading by the inclusion of clinically suspicious cases; on the other hand lowering of the rate may result through pick-ups being missed through faulty techniques; and now it must be stated a false pick-up rate may also result from the histological misinterpretation of dysplasia of the epithelium as intra-epithelial carcinoma.

Histological Interpretation

Many lesions show atypical epithelium which does not warrant a diagnosis of intra-epithelial carcinoma and this anaplastic epithelium may be found in the biopsy which has been preceded by a suspicious or positive smear. This entity is recognized and known by a variety of names: anaplasia, dysplasia, epithelial activity, basal hyperplasia, etc. With the present limited knowledge of the natural history of cancer it would be unwise to dismiss such anaplasias as benign. Many years ago (1914) Ewing stated "it is not true that a pathological condition must be either cancer or non-cancer. This process takes

time, sometimes years, and may be accompanied by very striking histological changes, which would be difficult to classify since they lie between inflammatory and anaplastic hyperplasia."

The more experienced the histologist, the smaller "the observer error" but even the most experienced in this particular field may well, and frequently do, disagree as to the interpretation of the border line case. Younge (1958) states: "There will always be a problem regarding the microscopic diagnosis of this lesion, that is, the interpretation of individual slides". With this philosophy, I would agree, provided the bias is towards conservatism.

Such cases of anaplasia are of great interest and follow-up by repeat smear and biopsy may well produce useful information on the natural history of carcinoma.

On occasion the pathologist may have been tempted to come down on the side of malignancy lest the patient's future be prejudiced by inadequate follow-up. There must be a limit, however, to the extent to which the patient may be subjected to repeated traumatization, both psychological and physical.

It therefore follows that to achieve a standard General and Absolute Pick-up Rate, the Clinician and Cytohistologist are equally involved. The former from clinical examination and experience has to decide the clinically suspect or potentially suspect, while the latter determines in the first instance the presence or absence of suspicious or positive cells from the smear, and of equal, if not more importance, the histological interpretation of where the normal ends and the abnormal begins.

Problem of the Patient

The positive smear followed by histological confirmation of intra-epithelial carcinoma should not in the younger and nulliparous age group demand radical, or semi-radical yet mutilating surgical interference, as was the tendency in the early days of cytohistological interpretation. A generous ring biopsy such as should have been obtained in the first place may be all that is necessary to remove the intra-epithelial lesion and this has been found repeatedly on examination of the cervix following total hysterectomy. Where the uterus has been conserved in view of youth and potential child-bearing, continuing supervision by repeat smears should be maintained. On the other hand, the parous patient approaching the menopause can be dealt with more radically and this, with justification, since there is greater freedom from psychological and physical sequelae.

The ultimate decision for what ever action is to be taken should have regard to the opinion given by the histologist, which opinion if to be of value should postulate either radical interference, limited interference, continuing supervision or "all clear". This symbiosis of clinician and pathologist demands mutual confidence and respect each for the other's opinion—the one clinical, and the other cytological and histological, and the closest liaison is essential if an effective service is to be established. Nothing can be more frustrating to the pathologist than to find advice ignored simply because the clinical findings would appear to be at variance. In such cases it should be possible, and both parties should be readily willing, that mutual discussion should take place so that the reason which prompts the opinion, and equally the reason which prompts the clinical action, can be reconciled. It is to be remembered that the whole purpose and justification of a cytological service is to present the diagnosis of malignant disease at the earliest possible time—it is hoped in the pre-clinical phase—since the prognosis to the patient is so much the better the earlier the stage at which diagnosis is made and appropriate treatment instigated.

Conclusion

Cytological diagnosis of pre-clinical cancer is as yet in its early days but already is of proven value when furnishing the "amber light", that usually is followed by the "red light" from ring biopsy, always remembering that radical treatment must only follow the "red light" and never the "amber" alone.

Comparisons of pick-up rates from different centres in this country or elsewhere can only be effective when there is a standard from which the figures are obtained and it is suggested that the

adoption of a "General Pick-up Rate" and more particularly an "Absolute Pick-up Rate" would remedy this discrepancy and reinforce the merits of a routine cytological service in gynaecological practice.

At the third National Cancer Conference held in Detroit in June, 1956, the opinion was held that "cytology is the most sensitive and exact method available for the detection of early cervical cancer", and Dr. Charles Cameron (1957), former Medical and Scientific Director of the American Cancer Society stated "we have reached the point where we believe that if uterine cancer cell examinations could be given to all adult women, loss of life from uterine cancer could be almost totally eliminated".

After these extremes of enthusiasm, however, it is right to quote Papanicolaou (1957), "In spite of great advances made in cytological diagnosis of cancer, we still have to depend on the biopsy as the most conclusive proof of cancer. A positive smear report is not a final diagnosis in itself. It does not eliminate the need for a careful clinical work-up and thorough examination of a tissue section by a qualified pathologist."

This authoritative opinion is endorsed by Sir Arthur Gemmell and the late Sir William Gilliatt (1956) who in summarizing a review of the subject undertaken by the Scientific Advisory Committee of the R.C.O.G. wrote: "We believe that it is impossible in the present state of our knowledge and of our experience in cytology, to accept a positive smear as establishing the diagnosis of malignant disease, but it is a compelling sign that further detailed investigation is urgently called for to confirm or disprove the suspicion which a positive smear produces."

ACKNOWLEDGMENT

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HYSTEROGRAPHY AND RUPTURED UTERUS

BY

VICTOR BOCKNER, M.R.C.O.G.

Department of Obstetrics and Gynaecology, University of Adelaide, Australia

IN a previous paper, Poidevin and Bockner (1958), it was shown that after Caesarean section the uterus always showed some deformity demonstrable on a lateral X-ray hysterogram. Moreover it was suggested that these deformities were the scar deficiencies resulting from Caesarean section. Amongst the cases so investigated a rupture of the uterus during a subsequent labour has occurred. The problem of forecasting what degree of demonstrable scar deficiency may be liable to rupture now becomes permissible. It is to this purpose that the following case history is presented.

CASE REPORT

The patient now aged 35 years had her first pregnancy in 1948 and delivered spontaneously a baby weighing 7 pounds 14 ounces. In 1950 in her second confinement she had a failed forceps, and Caesarean section was performed to deliver a baby weighing 9 pounds 2 ounces. At that operation a transverse incision placed well down in the lower segment was made, but during delivery of the foetal head the lower flap of the lower uterine segment split vertically in the midline extending downwards into the supravaginal cervix. Closure of the lower segment was difficult and subsequently she developed an infection of the pelvic tissues. In 1954, in her third pregnancy, X-ray pelvimetry revealed a normal pelvis and she was delivered spontaneously of a baby weighing 8 pounds 13 ounces, the labour lasting 21 hours. In 1956 a lateral hysterogram was performed; the film is shown in Figure 1. There is visible a large scar deficiency in the cervix starting from just below the internal cervical os and extending down the greater part of the cervical canal towards the external os. For comparison the lateral hysterogram of a normal uterus is shown in Figure 2.

She was next seen in 1958 in her fourth pregnancy. The hysterographic evidence of a large scar deficiency was discounted in favour of the previous successful vaginal delivery, and a further safe vaginal delivery was anticipated. Her pregnancy progressed uneventfully and she was admitted to hospital in labour at term. Presentation was cephalic, the head not engaged, the membranes were intact and the cervix dilated to admit two fingers. Labour continued during the next 30 hours but uterine contractions only became strong and regular during the last 5 hours. The membranes then ruptured and 15 minutes later there was a slight bright red blood loss *per vaginam*, and the foetal heart became irregular. Vaginal examination showed the presenting part to be high in the pelvis, the cervix dilated to admit four fingers and some blood clot attached to the anterior cervical edge. There was no prolapse of cord. The patient's general condition was good and she had no pain other than normal labour pains. Neither then nor at any time during labour had there been any tenderness over the lower uterine segment. Caesarean section was carried out forthwith. On opening the peritoneal cavity a large amount of free blood clot was present; this was cleared away to reveal a large rupture of the lower uterine segment. A stillborn foetus was extracted through the rupture. The bladder was identified quite intact and displaced deeply down over the vaginal vault, and total hysterectomy was performed. The uterine reflection of peritoneum

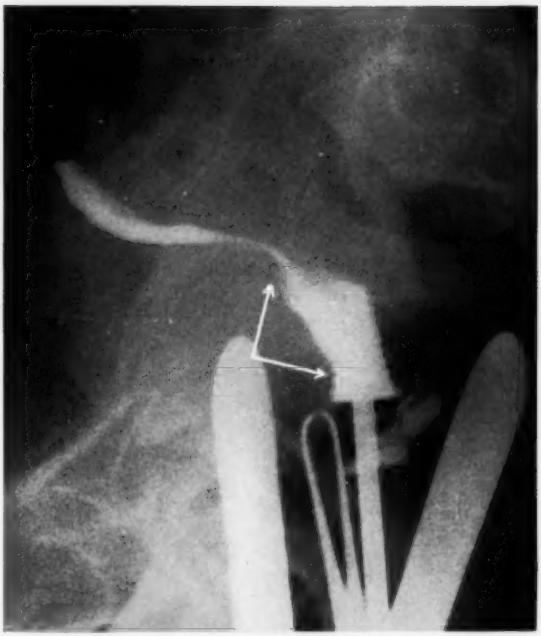

FIG. 1

Lateral hysterogram showing large scar deficiency in the cervix indicated by arrows.

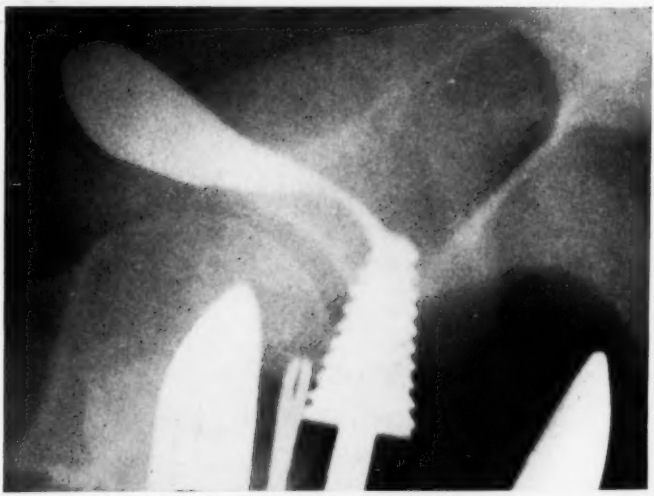

FIG. 2

Lateral hysterogram of normal uterus for comparison with Figure 1.

FIG. 3

Anterior aspect of uterus showing rupture in lower segment extending down the entire length of cervix.

FIG. 4

Ruptured uterus in sagittal section. The sites from where the histological sections were taken are indicated at A and B.

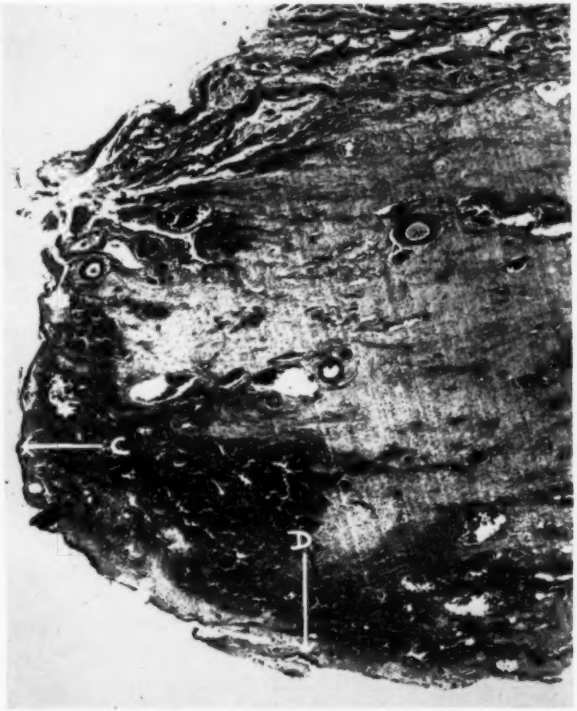

FIG. 5

Section taken at site A of margin of rupture. Indicated at C is well defined epithelial surface lining with occasional cervical gland indicated at D. ×75.

FIG. 6

Section taken at site B showing whole of ruptured area. Indicated at E is decidua-lined pocket running transversely across lower segment. Indicated at F is extravasation of recent blood cells. ×4.

was deficient and there was not enough peritoneum to cover the vault of the vagina after hysterectomy. Her post-operative recovery was apyrexial and completely uneventful.

The anterior aspect of the excised uterus is shown in Figure 3. The rupture in the lower segment is seen to extend down the entire length of the cervix. Figure 4 shows the uterus in sagittal section with the sites from which the histological sections were taken indicated. The upper and lateral margins of the rupture were rounded and relatively smooth, giving the appearance of an old-established opening in the lower segment, which in the fresh state was filled with well-organized blood clot. Figure 5, which is a section taken at site A, shows the margin of this opening to have a well-defined epithelial surface lining with occasional cervical glands. The deeper structure consists mainly of fibrous tissue and some muscle strands infiltrated with recent blood cells. Figure 6, which is a section taken at site B, is a low power magnification of the whole of the ruptured area. In its upper part it shows a well-marked pocket which ran transversely across the lower uterine segment, and is presumably the site of the previous lower segment Caesarean section. At the lower cervical part of the ruptured area there is seen an extravasation of recent blood into the tissues, and it was here only that evidence of recent tearing of the tissues was present.

Comment

On the findings outlined in this case it is reasonable to assume that there existed in this uterus prior to labour not only the transverse scar deficiency of the previous lower segment operation, but below it a large hole-like deficiency extending into the retro-vesical tissues. Referring to the appearances of the hysterogram taken before this pregnancy, the accurate interpretation of the film now becomes possible. It shows that a large scar deficiency in the anterior cervical wall was present prior to the pregnancy. Presumably it was caused by the inefficient healing of the inadvertent downward tearing at the previous Caesarean section. This deficiency is completely compatible with findings in the subsequent rupture of the uterus.

A further point of interest is that the hysterogram detection of scar deficiency was obtained after she had been through one uncomplicated vaginal delivery following Caesarean section. It may be presumed then that this scar deficiency was present before that vaginal delivery, but on that occasion the scar withstood the effect of labour although it ruptured with the next.

This case presents evidence that a large scar deficiency, which was visible on hysterogram, ruptured during labour. Hysterography after Caesarean section, therefore, is a practical and reliable method of investigation of the integrity of a uterine scar, and may be even more reliable than a history of previous safe vaginal delivery following Caesarean section. It is concluded that if a large deficiency is detected there exists strong presumptive evidence that the uterus is liable to rupture in a subsequent labour, and delivery by Caesarean section is indicated.

Summary

(1) In a patient previously subjected to Caesarean section, hysterogram investigation revealed a large scar deficiency.

(2) Rupture of the uterus occurred in labour through this scar deficiency.

(3) Hysterography after Caesarean section is a practical investigation allowable of reliable prognostic interpretation.

Acknowledgments

To Dr. F. L. Thyer I am indebted for information of the patient's Caesarean section in 1950. To Dr. R. McIntosh, under whose care the patient was during her last two confinements and who performed the Caesarean hysterectomy, I am indebted for permission to report this case.

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THE INCIDENCE OF TWINS AND THEIR STILLBIRTH RATE OVER THE LAST HUNDRED YEARS IN THE NEGRO POPULATION OF ANTIGUA

BY

K. H. UTTLEY, M.A., M.D., D.T.M.&H.
Senior Medical Officer
Antigua, West Indies

INTRODUCTION

A GENERAL description of the geographical and ethnic characteristics of Antigua, of its censuses over the last century, and of the efficacy of the Births and Deaths Ordinance introduced in 1856, has been given in a previous number of this journal (Uttley, 1959) and need not be recapitulated here. It is sufficient to state that this paper is based on the material collected by a scrutiny of all the parish registers since 1857, the first complete year following the introduction of compulsory births and deaths registration, which included stillbirths.

ANALYSIS OF THE MATERIAL

During the century there were 133,152 live and stillbirths among the coloured people of this colony; among these there were 2,053 pairs of twins, or one pair to every 65 pregnancies. The author has not been able to find a series of statistics of twins born elsewhere in the West Indies for comparison, excepting that in a sequence of 5,526 deliveries in the labour wards of the University College Hospital of the West Indies, Jamaica, there were 96 sets of twins or one set in 57·6 pregnancies (Stewart, 1958). The two series are however hardly comparable, in that the hospital figures contain data from persons of several ethnic types, and are affected by the usual factors that are inseparable from hospital statistics.

In my series there was also one set of triplets to every 6,048 pregnancies.

The following table shows the incidence of twins in successive decades since 1857:

TABLE I

Antigua, 1857–1956. Incidence of Twins

Decades	Twin Pregnancies Per 1,000 Total Births	
1857–1866 ..	15·5	or one in every 64 pregnancies
1867–1876 ..	16·4	or one in every 61 pregnancies
1877–1886 ..	14·9	or one in every 67 pregnancies
1887–1896 ..	21·0	or one in every 48 pregnancies
1897–1906 ..	18·5	or one in every 54 pregnancies
1907–1916 ..	14·6	or one in every 68 pregnancies
1917–1926 ..	15·4	or one in every 65 pregnancies
1927–1936 ..	13·3	or one in every 75 pregnancies
1937–1946 ..	12·6	or one in every 80 pregnancies
1947–1956 ..	14·4	or one in every 69 pregnancies
Average for the century	15·4	or one in every 65 pregnancies

RATIO OF MONOZYGOTIC TO DIZYGOTIC TWINS

Among the 2,053 pairs of twins in this series there were 1,285 pairs of the same sex and 768 of unlike sex. Bulmer (1959) has written: "The ratio of monozygotic and dizygotic maternities can be calculated by Weinberg's method (1909) which assumes that dizygotic twins are equally likely to be of the same or of different sexes;

monozygotic twins must of course be of the same sex. If therefore, L like-sexed and U unlike-sexed twin maternities are observed, the number of dizygotic twin maternities is taken as 2U and the number of monozygotic twin maternities as L-U."

In the Antigua data L=1,285, U=768, and L-U=517; expressing these as per 1,000 maternities: the number of monozygotic maternities per 1,000 maternities is 11·7, and the number of dizygotic twin maternities is 3·9, over the century.

Stillbirth Mortality in Twins

The stillbirth mortality among this series of twins is of interest. In the following table the twin births are grouped according to type, that is by the number of live births and stillbirths of each sex, with the corresponding data for England and Wales for 1939–1941 for comparison.

Group 2 contains only the dizygotic or dissimilar twins born during the period; the other two groups contain a mixture of monozygotic and dizygotic twins. The table shows that the stillbirth rate in twin male pregnancies, 122 per 1,000, is higher than that for twin female or mixed twin pregnancies. In England and Wales on the other hand the rate for twins of like sex, whether male or female, is higher than those for twins of different sexes.

There is another matter of interest that emerges from a study of Table II. To quote from and enlarge upon Sutherland (1949, p. 34) and substituting my data for his: There is a very definite association between stillbirth in one twin and stillbirth of the other. The expected numbers of confinements in which both foetuses were stillborn, if this association did not exist, are shown in the table.

The method of calculation of this expected figure is best illustrated by an example: In Group 1 there are 650 twin confinements, namely 548+46+56=650. Among these 1,300 infants there were 158 stillbirths, i.e., 46 of type LMSM (1 live male and 1 stillborn male), and 2×56 of type 2SM (i.e., 2 stillborn males); this gives a stillbirth rate of 122 per 1,000.

The chance of having one stillbirth at a confinement of twins was therefore 122 in 1,000 or 0·122 per confinement. The chance of both twins in a confinement being stillborn therefore would be $(0·122)^2$ if there were no association between the fates of the two. Therefore in the whole of Group 1 with its 650 confinements the expected number of those where both twins are stillborn is $(0·122)^2 \times 650 = 9·67$.

Actually there were pairs of stillborn twins in 56 cases, as will be seen in the last line of Group 1, and this gives an actual divided by the expected rate of 5·8, i.e., 56÷9·67=5·8.

Similarly in Group 2, the number of stillbirths was 29+37+(2×47)=160; this gives a stillbirth rate of 104 per 1,000 births among the 768 pairs of twins. The reasoning given above produces a ratio of actual to expected

Table II

Stillbirth Rates in Twin Confinements, by Type

	Antigua, 1857–1956						England and Wales, 1939–1941*				
Group	Type of Twin Pregnancy	Number of Confinements: Actual	Number of Confinements: Expected	Actual÷Expected	Stillbirth Rate		Type of Twin Pregnancy	Number of Confinements: Actual	Number of Confinements: Expected	Actual÷Expected	Stillbirth Rate
1	2LM 548 LMSM 46 2SM 56		9·67	5·8	122		2LM 6,269 LMSM 580 2SM 299		49	6·1	82·4
2	LMLF 655 LMSF 29 SMLF 37 SMSF 47		8·32	5·6	104	Among males =109 Among females =99	LMLF 6,955 LMSF 271 SMLF 322 SMSF 135		24	5·6	56·2	Among males =59·5 Among females =52·8
3	2LF 552 LFSF 46 2SF 37		5·61	6·6	94		2LF 6,226 LFSF 517 2SF 177		27	6·6	62·9

* Data from Sutherland (1949), p. 35.

In this Table: L=live birth; S=stillbirth; M=male; F=female.

of 5·6. The argument for Group 3 follows the same lines.

The ratios in Antigua vary somewhat from those of England and Wales, but the association discussed is exemplified in the coloured people of Antigua as in the English people.

Among these 4,106 infants, the stillbirth mortality in males was 117, in the females it was 96, with an overall mortality of 107, there being 242 male and 196 female stillbirths in the series. Expressed differently, males constituted 55·3 per cent and females 44·7 per cent of the stillbirths in twins, or the ratio was 1,235 males to 1,000 females; England and Wales (1939–1941) being 1,125 (see Sutherland, p. 35).

In order to place the statistics about twins in Antigua in proper perspective, the following are the Island's birth statistics of the coloured people for the century 1857–1956:

Total male live births	62,175
Total female live births	60,139
Total male stillbirths	5,874
Total female stillbirths	4,964
Stillbirth rate per 1,000 total births ..	81
Males per 1,000 females (live births)	1,034

Summary and Conclusions

A survey of all the twin pregnancies recorded in the negro population of Antigua, West Indies, over the hundred years 1857–1956 shows that, in 133,152 live and still births, there were 2,053 pairs of twins, or one pair in 65 pregnancies.

The incidence of triplets was one set in 6,048 pregnancies. Among the 4,106 infants born, the stillbirths (242 males and 196 females) gave a stillbirth rate of 107 per 1,000 as compared with a rate of 81 in the century's series of all births. In males the rate was 117, in females it was 96 per 1,000.

The dizygotic twin maternity rate was 11·7 per 1,000 maternities, and that for monozygotic twin maternities was 3·9 per 1,000 maternities.

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ADVANCED EXTRA-UTERINE GESTATION

A Clinical Report on Eight Cases

BY

PREMA M. NAIDU, M.D., F.R.C.S.(Edin.), F.R.C.O.G.
Professor of Obstetrics and Gynaecology

AND

UMESH N. REDDY, M.B., B.S.
Gynaecological Registrar
Osmania Medical College, Hyderabad, A.P., India

THE literature contains several excellent reports of personal or collected series of abdominal and other advanced ectopic pregnancies. Papers by Ware (1948), Cross *et al.* (1951), Barrett (1952), King (1954), Charlewood and Culiner (1955) and Yahia and Montgomery (1956) give detailed results of the outcome in such pregnancies. Our recent experience with a rapid succession of advanced extra-uterine pregnancies is the occasion for the publication of this report. Although the first case was seen exactly 10 years ago, and the second was met with two years back, the remaining 6 cases were operated upon within a short span of 12 months, the last case being dealt with during the course of writing this report. An extra-uterine pregnancy was termed as advanced by Rajoo and Maddimsetti (1943) and Clark and Bourke (1959) when the pregnancy is over 12 weeks and by Mitra (1942) when the gestation is more than five and a half months. But King (1954) preferred the foetus to have reached 28 weeks development before so grouping it.

MATERIAL

These eight cases of extra-uterine pregnancies of 28 weeks and over were seen during a period of 9 years and 11 months from August, 1949 to June, 1959 at the Associated Hospitals of the Osmania Medical College, Hyderabad. The total number of ectopic pregnancies operated upon in these hospitals in the year January–December, 1958 was 57. The total number of deliveries for the same period was 13,842.

CASE REPORTS

Case 1

A.B. (587), aet. 32 years, was admitted on 10th August, 1949 for delivery as a gravida-4 at term. On the 15th, she complained of vague pains in the abdomen followed by intense shivering. Three hours after the onset of the discomfort vaginal examination revealed a non-pregnant cervix and a uterus corresponding to 10–12 weeks. Though no X-ray study was then possible, an advanced extra-uterine pregnancy was diagnosed because of the ease with which the foetus could be palpated. Half an hour later, at laparotomy, a full-time foetus was found in the peritoneal cavity, showing sluggish movements. On delivery, though the heart was beating faintly, the infant could not be revived. This was found to be a normally developed male infant weighing over 7 pounds. Traces of an amniotic sac, as represented by greenish patches of membranes each about 3×4 cm. in size were found pasted to the parietal peritoneum here and there, and over the pelvic colon. The cord was traced to a normally sized placenta with a normal foetal surface and attached to the pelvic organs, chiefly on the left and to the bifurcation of the aorta and common iliac vessels. The umbilical cord was tied near the placenta and severed. The placenta was left undisturbed for fear of severe haemorrhage. The patient made an uneventful recovery.

She returned to the hospital 12 weeks later. The abdomen felt normal except for a thickening below the umbilicus on deep palpation. At the earnest request of the patient, who knew that the placenta had not been removed, a second laparotomy was undertaken. There

were no adhesions, and the patches of membranes had disappeared. The lower part of the uterine body could now be seen between the bladder and the lower margin of the placenta. The latter was greenish in colour and had shrunken to nearly half its original size, though it appeared thicker. A cautious effort to remove it resulted in its easy separation at a plane of cleavage found between the placenta and the uterine wall. On removal of the placenta, a rosette of granular tissue about 2 cm. in diameter was noted on the left cornu of the uterus, above and behind the uterine insertion of the tube, suggesting an interstitial origin of the pregnancy. Total hysterectomy with left salpingo-oöphorectomy was performed. The peritoneum over the large vessels presented a shaggy appearance with scattered pin-point oozing. Convalescence was uneventful.

Case 2

Z.B. (1330), aet. 25 years, a gravida-2 was admitted on 12th November, 1957, with the history of amenorrhoea for 6½ months and abdominal pain with slight bleeding *per vaginam* for 8 days prior to admission. She also gave a history of having had a Caesarean section for arm prolapse 2½ years earlier, followed by a hectic temperature which had lasted for 40 days. She looked ill, the pulse rate was 100/minute, the temperature 100° F. and the blood pressure 120/90 mm. Hg. Abdominal palpation revealed a swelling corresponding to a 28-weeks pregnancy. Foetal parts were not felt, and a foetal heart could not be heard. There was tenderness all over the swelling, which was rather firm. By vaginal examination the os was found to be closed and the cervix not taken up. A provisional diagnosis of accidental haemorrhage was made. Induction of labour with intravenous pitocin drip was instituted, but was discontinued as there was no response by palpable hardening.

The laboratory report the next day was: haemoglobin 50 per cent, red cell count 2·8 million per c.cm., white cell count 11,800 per c.cm. with polymorphonuclear leucocytosis. The erythrocyte sedimentation rate (1st hour) was 65 mm. The clot observation test was normal. The above findings called for a revision of diagnosis. X-ray taken two days later (Fig. 1) showed a definite Spalding's sign. The foetus appeared poised across the upper abdomen in a transverse lie with its limbs hanging downwards on each side of a central mass, clearly indicating its extra-uterine position. These findings pointed to a possibility of a rupture of the previous Caesarean scar early in pregnancy with partial escape of the foetal sac into the peritoneal cavity with continued growth of the foetus. The patient's condition indicated that infection of the sac was present. Laparotomy was considered but was deemed unsafe as her temperature remained elevated in spite of antibiotics. Hysterogram (Fig. 2) at this stage revealed that the opaque material had escaped into the peritoneal cavity showing the extra-uterine position of the foetus. Eight days later she developed marked ascites and gross oedema of her feet. She was rapidly becoming toxic and emaciated. The temperature continued to swing. The original blood-stained vaginal discharge had turned dirty green, shreddy, offensive and profuse, amounting to several ounces a day, confirming placental disintegration inside the uterus. A uterine sound reaching to a depth of 18–20 cm. also indicated that the uterus was unduly enlarged due to the presence of the placenta. An X-ray taken five weeks later showed a pyriform shadow containing gas and the dismembered foetal skeleton.

Eight weeks later, the patient passed two pieces of long bones of the foetus per rectum, though pelvic examination showed no fistulous formation in the lower rectum or in the vaginal vault. X-ray (Fig. 3) nine weeks after admission showed continued evidence of gas in the sac. Palpation of the umbilical region elicited crepitus and a bag of bones was felt under the skin. The patient did not rally despite repeated small blood transfusions and her condition steadily deteriorated. She became excitable and was taken home, where she is reported to have died about four months from the time of admission.

Case 3

K. (438), aet. 30 years, gravida-2, was admitted on 23rd June, 1958, with a history of six-months amenorrhoea and bleeding *per vaginam* for twenty-four hours. On further enquiry, she admitted having had a bout of bleeding following a period of two-months amenorrhoea which she did not regard as having any relation to the present pregnancy. The patient was restless and pale with signs of intraperitoneal haemorrhage.

On laparotomy a large quantity of free blood was found. There was a mass on the left side continuous with the uterus. Glistening through the anterior aspect of the broad ligament, the placenta could be seen. The omentum was attached to the posterior aspect of this mass, When it was separated, the membranes became visible. But, on an attempt to explore the sac, the membranes ruptured and the foetus escaped. The foetus appeared recently dead and of about 28-weeks gestation. The round ligament was found attached lateral to and below the sac. The left tube was stretched on the roof of the sac. The ampullary part of the tube and the ovary were found laterally not far from the root of the round ligament of the same side. Mesially, the sac appeared to be hypertrophied and muscular incorporating the lateral wall of the uterus. Because of this, total hysterectomy was performed, removing the sac and the uterus *en bloc*. This appeared to be a case of advanced extra-uterine gestation originating in the interstitial part of the tube and developing as an intra-ligamentous pregnancy after primary rupture. Finally, an intra-peritoneal rupture of the intra-ligamentous pregnancy had brought her to the hospital in a collapsed state. The microscopic section taken from the roof of the sac goes to prove its tubal origin.

Case 4

N. (16801), aet. 35 years, a para-4, was admitted on 10th November, 1958, with a history of four-months amenorrhoea and difficulty in passing urine for fifteen days. On abdominal palpation, a mass was found rising up to the umbilicus, chiefly on the right side. *Per vaginam* the surface of the mass was noted to be hard

FIG. 1

Case 2. Skiagram showing Spalding's sign and a transversely placed, highly poised foetus.

FIG. 2

Case 2. Hysterogram showing escape of opaque material into the peritoneal cavity.

FIG. 3

Case 2. Skiagram showing gas in the foetal sac. No foetal bones are noted.

FIG. 4

Case 4. Hysterogram showing normal outline of the uterus and the extra-uterine position of the foetus.

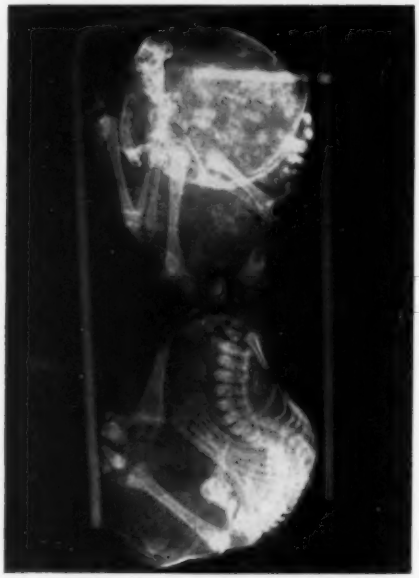

FIG. 5

Case 4. Skiagram of the cut specimen indicating foetal maturity.

FIG. 6

Case 5. Straight X-ray shows ball formation.

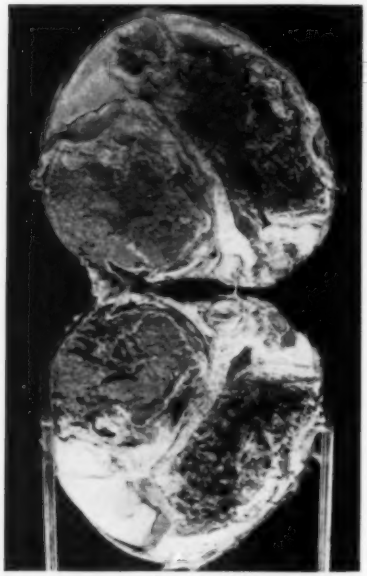

FIG. 7

Case 5. Cut section of the rudimentary horn showing mummification.

FIG. 8

Case 7. Specimen of gestation sac with windows showing foetal parts and the relation of the medial third of the tube.

FIG. 9

Case 8. Picture showing relations of the distended rudimentary horn to the uterus and adnexa.

FIG. 10

Case 8. Picture taken just after excising the rudimentary horn.

FIG. 11

Case 8. Skiagram of the rudimentary horn showing foetal maturity and soft tissue shadow of the sac wall.

and irregular, suggestive of a calcified fibroid. The uterus was palpable separately on the left side, normal in size. Hysterogram indicated the presence of an extra-uterine foetal sac (Fig. 4).

At laparotomy, the relation of the extra-uterine sac to the fimbrial end of the right tube suggested a tubo-abdominal pregnancy. The sac, the size of a full-term foetal head, was found embedded in dense adhesions of the omentum. It had a shaggy appearance outside. The mass was excised by incising through the stretched tube on the uterine side. The cut surface of the mass removed after fixation showed the colour differences of the various tissues of the mummified foetus. The corresponding skiagram (Fig. 5) of the specimen shows that the bones are those of a near-term foetus.

Case 5

R. (14252), aet. 30 years, a multipara, was admitted on 22nd September, 1958, with a history of five-months amenorrhoea and bleeding *per vaginam* of one day's duration. Examination revealed a mass rising up to the umbilicus. On bimanual examination, the mass was palpable through the anterior fornix and gave a peculiar corrugated feel suggestive of the foetal thoracic cage. A normal sized uterus was palpated posteriorly. Straight X-ray (Fig. 6) and hysterogram confirmed the presence of an advanced extra-uterine foetus.

At laparotomy, the parietal peritoneum and the omentum were found to be adherent to the mass. On separation of these, an almost rounded mass was seen lying to the right side attached by a short broad band to the lower end of the uterine body at the level of the internal os. The band was in juxtaposition to the ovarian ligament, the tube and the round ligament. The mass was recognized as the rudimentary horn and the uterus as unicornuate. There was no canalization of the rudimentary horn in which the pregnancy was situated. The corpus luteum was found in the ovary of the opposite side indicating transmigration of the ovum.

The surface of the tumour was studded with bony prominences suggestive of a litho-kelyphos. The gestation sac was removed by clamping and dividing the band. The round ligament was divided close to the ovarian ligament and was re-implanted into the right side of the uterus which was typically unicornuate. The cut surface of the specimen (Fig. 7) also depicts the end stage of mummification in the various tissues of the foetus. The skiagram of the specimen showed a well-developed foetus.

Case 6

R. (7937), aet. 40 years, was admitted in June, 1958 because of a swelling in the abdomen of 6-months and an amenorrhoea of one year's duration. Abdominal examination revealed a mobile hard tumour rising to the umbilicus. On bimanual examination, the uterus was felt separately from the mass and enlarged to about a 10-weeks size. A provisional diagnosis of subperitoneal fibroid was made.

On laparotomy both adnexa were found to be normal. A tumour, the size of a foetal head, appeared to be a subperitoneal fibroid seated on the fundus of the uterus on the right side and attached to it by filamentous adhesions. These yielded readily to finger dissection. The surface of the tumour was fairly smooth and only on cut section was it recognized to be a foetal sac of an advanced extra-uterine pregnancy. X-ray showed the foetal age to be almost forty weeks.

Case 7

F.B. (876), aet. 25 years, gravida-3, was admitted on 5th May, 1959, with a history of seven-months amenorrhoea followed by bleeding on and off *per vaginam* for one month. On admission, her general condition was fair. Abdominal palpation revealed a mass rising up to the umbilicus and occupying the left half of the abdomen. Palpation suggested the presence of foetal parts. Foetal heart sounds were not heard. On vaginal examination, the cervix was drawn up and soft in consistency. The uterus, which was found to be bigger than normal, was palpated midway between the symphysis and umbilicus on the right side. A rounded mass was found filling the pouch of Douglas and was continuous with the globular swelling felt per abdomen on the left side. The uterine sound could be passed to a depth of 4½ inches. A diagnosis of extra-uterine pregnancy was made and this was confirmed by the hysterogram.

On laparotomy, a large extra-uterine gestation sac was seen occupying the left lower part of the abdomen and nearly half of it was found extending into the pouch of Douglas. It had contracted dense and highly vascular adhesions with the uterus and the large bowel. The medial two-thirds of the left tube could be traced from the left cornu of the uterus to the summit of the tumour. The lateral one-third of the tube was found to be dilated and incorporated with the mass. The left ovary was normal in size and in normal relation to the uterus on the posterior aspect of the sac. The round ligament was also in its normal situation. The right tube was found to be distended with serous fluid and its fimbrial end occluded. Between the sac and the posterior surface of the uterus there were markedly prominent veins which gave way even to the lightest touch thus occasioning heavy bleeding. Vascular omental adhesions were found posteriorly and to the left.

The sac was removed entire by clamping and by dividing through the ovarian ligament and the uterine end of the tube, the broad ligament medially and the infundibulo pelvic ligament laterally.

Separation of the adhesions between the mass and the uterus, the omentum and the pouch of Douglas, caused severe haemorrhage. The patient was severely shocked at the end of the operation and expired ten hours later. A transfusion of 600 ml. of blood had been given during the operation. Skiagram of the specimen revealed a foetus of about 30-weeks maturity. A photograph of the specimen is shown in Figure 8.

Case 8

C. (8021), aet. 30 years, was admitted on 17th June, 1959, with a history of eight-months amenorrhoea. Foetal movements had stopped a week earlier. She was

a gravida-7, each of the previous six pregnancies having ended prematurely at the seventh month, and by breech delivery. Abdominal palpation revealed a firm ovoid swelling the size of a 28-weeks gestation on the right side of the midline.

Foetal parts were not palpable and foetal heart sounds were absent. On vaginal examination, the cervix was found to be long but soft, and the internal os was patulous. The abdominal swelling did not move freely on movement of the cervix. Another hard swelling the size of a pear was felt on the left side in continuation with the cervix, suggestive of a non-gravid uterus. The oval mass containing the foetus was firm and no relaxation was demonstrable. The asymmetrical position of the foetus in the abdomen, taken in conjunction with the firmness of the swelling, suggested an ectopic gestation. A skiagram showing Spalding's sign confirmed foetal death. Hysterogram revealed the uterus to be of normal size and lying to the left. Further the skiagram demonstrated a soft tissue shadow around the foetus pointing to a pregnancy in a rudimentary horn.

On laparotomy a well-developed horn of the uterus was found on the left side, continuous with a large smooth ovoid muscular swelling on the right side, measuring $14 \times 12 \times 12$ cm. The right tube, the right ovary, the ovarian and round ligaments were found to be attached to the extreme right of the mass (Fig. 9). The round ligament had spread out over the mass with its veins markedly dilated and shining under the peritoneum. The findings and her history suggested a bicornuate uterus with pregnancy in one horn. There were no adhesions, the surface being smooth. The utero-vesical fold of peritoneum below this mass was empty, allowing the finger to identify the supra-vaginal cervix to be normal in shape and belonging to the non-gravid horn on the left. An incision was made from the fundus along the septum on the enlarged side with the intention of excising the septum. On exploring with a finger, the cavity of the sac was made out to be in a rudimentary horn with no communication with the cavity of the main horn of the uterus.

The rudimentary horn containing the gestation sac was excised (Fig. 10), injury to the main horn being prevented by guiding the dissection with the finger in the rudimentary horn. Uterine vessels were met with on the right side of the cervix below this horn. The raw surface of the uterus on the right side was repaired in three layers, as after myomectomy, with 2/0 catgut. The uterine cavity was not opened. An attempt was made to restore normal relations by fixing the round ligament to the blind cornu and the anterior and posterior flaps of the broad ligaments to the side of the uterus over the repair. Skiagram of the excised sac (Fig. 11) confirmed the maturity of the foetus to be about 30 weeks and revealed the soft shadow of the thick muscular wall which encased it.

The eventualities of the above cases are summarized in Table I.

Summary

(1) Eight cases of advanced extra-uterine pregnancy of various types are reported with their respective outcome.

(2) Difficulties in diagnosis and the common diagnostic aids are discussed.

(3) The safety of leaving the placenta *in situ* is indicated.

Table I

Eight Cases of Advanced Extra-Uterine Pregnancy

Case	Dates	Age	Period of Gestation	Parity	Types of Pregnancy		Mother	Foetus
					Primary	Secondary		
1 ..	10. 8.49	32	40 weeks	3	Interstitial	Abdominal	Alive	Neonatal death.
2 ..	12.11.57	25	28 weeks	1	Uterine	Abdominal	Dead	Skeletonized.
3 ..	23. 6.58	30	28 weeks	1	Interstitial	Intraligamentous (secondary rupture at time of admission)	Alive	Dead
4 ..	10.11.58	35	28 weeks	4	Right tube (fimbrial end)		Alive	Mummified.
5 ..	22. 9.58	30	28 weeks	9	Rudimentary horn		Alive	Commencing calcification.
6 ..	12. 6.58	40	40 weeks	3	Abdominal		Alive	Mummification
7 ..	5. 5.59	25	30 weeks	2	Tubo-abdominal		Dead	Dead.
8 ..	17. 6.59	30	30 weeks	6	Rudimentary horn		Alive	Dead.

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UNUSUAL FORMS OF GYNATRESIA

BY

C. ROY MACDONALD, M.B., F.R.C.S.E., F.R.C.O.G.
Grimsby General Hospital

EXAMPLES of partial or complete atresia of the genital tract are not infrequently encountered in gynaecological practice. They may arise from developmental defects, the result of incomplete fusion or canalization of the Müllerian ducts, or may be due to occlusive disease or operative procedures.

Of the congenital variety some are silent and undiscovered until puberty or even later; others provoke acute symptoms calling for urgent surgery.

During the last few years I have met with two unusual conditions, interesting clinically because their recognition leads to a logical and safe operative approach with rapid relief of symtoms. The first is a combination of uterus didelphys and double vagina, the lower segment of one half of the genital tract being closed with resultant unilateral haematocolpos, the opposite side being patent allowing menstruation from one horn of the uterus to occur. The rarity of this condition is borne out by a study of the literature. Embrey (1950), describing a case of his own, drew attention in a comprehensive survey to the confusion of nomenclature in the early writings on this subject, making it difficult to distinguish its true incidence. He quoted Brown and Brews (1930) who found only one case in a review of 50 cases of cryptomenorrhoea. Later, Brews (1957), from case records at the London Hospital, extending back 60 years, discovered only 5 cases, the closed sac being present in 4 cases on the right side and once on the left. Other individual cases have been reported by Purslow (1922), St. George Wilson (1925), Simon (1928) and more recently by Gibberd (1957) and Hill (1958).

The ages of patients reported from all sources ranged from 12 to 17 years. The symptoms arose within 4 months to 2 years from the onset of menstruation and were generally those of increasingly severe dysmenorrhoea, backache, pain "in the seat" and difficulty in voiding urine. The pain is sometimes, but not always, localized to one side of the lower abdomen, and may be sufficiently acute to constitute a surgical emergency.

On examination, there is usually a unilateral pelvic swelling to be felt. As might be expected in the light of the close connexion between the development of the genital and urinary systems, abnormalities of the latter are not infrequently found in association with this condition, the commonest being the absence of the kidney and ureter on the side of the haematocolpos. Of the cases reported in the literature few, if any, appear to have been recognized before operation, and many had a laparotomy performed as a primary procedure. In several, including the case described by St. George Wilson (1925), the bicornuate uterus and haematocolpos were removed in one piece.

It is part of the purpose of this paper to draw attention to the recognition of this condition and the fact that it can be treated successfully with less risk from below.

Case 1

J.L., aged 15½, was referred to the Hospital Out-Patient Clinic in November, 1942, on account of lower abdominal pain, more acute during menstruation. Periods had commenced at the age of 13 and were regular, 4–5/28.

There was no history of bowel or urinary symptoms. Abdominal examination was negative; the hymen was

intact; rectally one could feel a tense, tender ovoid swelling lying in front to the left of the midline.

She was admitted to hospital, and, under general anaesthesia, the hymen was incised allowing the cervix to be visualized high up in the vault. There was a brown discharge from the os. The left antero-lateral vaginal wall in its upper half presented a swelling about the size of a goose's egg, the long axis being parallel to the vagina. The uterus could not be palpated.

The swelling was incised along the whole of its length, and about 3 ounces of thick, chocolate-coloured fluid evacuated, the cavity being packed with flavine and glycerine gauze. She was subsequently discharged from hospital and seen at regular intervals for one year, at the end of which the cavity was found to have remained open.

In February, 1944 she was re-admitted with a history of a dull pain in the right lower quadrant of the abdomen thought to be due to a sub-acute appendicitis. It was only then that the presence of a bicornuate uterus was suspected. Before referring her to a general surgeon investigation of the urinary tract was carried out.

Excretion urography showed a functioning right kidney with some dilatation of its pelvis and upper ureter. The left urinary tract was not seen. Cystoscopy and an indigo-carmine test confirmed the absence of the left ureteric orifice. The right ureteric orifice was larger than normal. An appendicectomy was later performed by a general surgeon.

At operation he found a bicornuate uterus with some dilatation of the left horn and closure of the fimbriated end. The right kidney was hypertrophied and the left absent.

She was lost sight of until 1950, when I saw her again in another town 30 miles away on account of backache. She was then 23 years of age, had been married for 3 years and been delivered of a child, aged 14 months. Menstruation was regular, 5–6/28, and painless. A bicornuate uterus with twin cervices could then be readily distinguished. There was some laxity of the vaginal walls. A ring pessary was inserted and later she was referred to an orthopaedic surgeon. She then passed out of my care.

Case 2

S.G., a schoolgirl, aged 14, was first seen at her own home on 25th October, 1950, as an emergency, on account of acute colicky right-sided lower abdominal pain of some 5-weeks duration. Periods had been present for 9 months, and had always been painful, the discomfort continuing throughout the loss. Between periods she had been relatively comfortable until the recent episode. She had complained of slight nausea but no vomiting; her bowels were rather constipated, and she had suffered from frequency of micturition for 4–5 days. Her own doctor had made a diagnosis of twisted ovarian cyst.

On examination, she looked a little distressed. Temperature 99°, pulse 116. A tender, rounded swelling was felt in the right lower quadrant of the abdomen just above the pelvic brim, surmounted by a slightly mobile small firm mass. There was a little voluntary muscular rigidity. The patient was a virgin and rectal examination revealed a tense ovoid cystic swelling lying to the right of the midline, the lower pole of which descended into the pelvis. A diagnosis of right unilateral haematocolpos was made and the patient admitted to hospital. Under general anaesthesia the previous findings were confirmed, the swelling lying parallel to the vagina being about four to six inches long and projecting into its anterior and right lateral walls. It seemed continuous with the anterior lip of the cervix which admitted the tip of a finger and through which a sound passed to the left for 2½ inches. The limits of the bladder wall were also defined by a sound and it was found that the cystic mass lay alongside it. A longitudinal incision was made in the right vaginal wall, resulting in the out-pouring of about half a pint of a dark red fluid of a treacle-like consistence. The resultant smooth-walled cavity was found to extend from about the level of the hymen upwards, backwards and in front almost to the urethra. There seemed to be a depression at its apex but a second uterine horn could not be definitely demonstrated.

A portion of the septum was obtained for section, and the pathologist reported on it as follows:

"One surface of this tissue is covered by a single layer of columnar epithelial cells, the other by squamous epithelium. The fibrous sub-epithelial layer on both sides contains a patchy mild, and mainly chronic inflammatory infiltrate. The central bulk of the tissue consists of smooth muscle bundles." An excretory urogram showed enlargement of the left kidney "consistent with physiological enlargement". The right kidney was not identified.

Cystoscopy later confirmed the absence of the right ureteric orifice, the left being normal in size, shape and position; it admitted a catheter to a length of 25 centimetres, and through it indigo-carmine injected intravenously was excreted in 7½ minutes.

The patient was discharged and reported two months later. She had had two periods in the interval which were quite painless, each lasting 5–6 days. The vagina admitted 2 fingers readily. There was a centrally placed cervix. The wall of the cavity had contracted down to a small cul-de-sac in the right angle about 1½ inches long. A bicornuate uterus was easily palpated, the right horn opening into the cul-de-sac and measuring by sound about 1½ inches. The cervices were separated by a solid bridge of tissue. On 26th April, 1955, that is 3 years later, she was referred back to the clinic on account of amenorrhoea of 14-months duration. In the interval she had been treated by an orthopaedic surgeon for spinal scoliosis.

She was then a thin slender girl with flat breasts and narrow sub-costal angle, the body hair being typically feminine. The pelvic findings had not changed. Repeated courses of oestrogen therapy were advised but she did not return.

Case 3

B.G., aged 13, a schoolgirl, was admitted on 24th July, 1952, complaining of deep-seated pain in the right buttock which commenced 10 days previously as vague

lower abdominal discomfort radiating posteriorly. It was now constant with acute exacerbations. Menstruation had begun 4 months before admission and the present period had lasted for 10 days. The previous losses had been accompanied by only slight discomfort. There were no bowel or urinary symptoms.

On examination she was found to be a healthy-looking girl with slight right-sided lower abdominal tenderness. She was a *virgo intacta* but bulging of the right wall of the vagina could be seen, the epithelium having a bluish tinge. On 25th July, 1952 under general anaesthesia the hymen was incised, and the swelling opened, liberating about 10 ounces of chocolate-coloured fluid. The report on intravenous urography read as follows:

"Right kidney and ureter not identified. No apparent excretion."

The patient was seen again on 26th September, 1952; in the interval she had had two normal periods and was symptom-free.

The second condition I wish to describe is that of hydrocolpos or hydrometrocolpos, in which the vagina and sometimes the uterus becomes distended by fluid other than blood, usually owing to the presence of an obstructing membrane in the region of the hymen.

Commandeur (1904) was apparently the first to draw attention to this condition, describing one case of his own and reviewing 9 others in the literature. It has been reported in infants from birth to 11 weeks old by Spencer (1916), Mahoney and Chamberlain (1940), Morris (1945) and Sen (1949), and in young girls just before puberty, by Bowen (1941), Maliphant (1948) and Brews (1957). Rea and Theron (1957) traced 22 cases in the literature and added one of their own. Morris (1945) cites a case described by Markus occurring in a woman of 72 years, following vaginal stenosis of inflammatory origin. The cystic swelling thus formed may displace the uterus, bladder and bowel causing pressure symptoms, such as retention of urine, constipation, diarrhoea, and even blood in the stools. There may be partial obstruction of the ureters and bilateral hydronephrosis as in the case of a 7-weeks old infant described by Morris (1945). This child also had oedema and cyanosis of the lower limbs.

In one of the cases reported by Mahoney and Chamberlain (1940) there were associated developmental anomalies including imperforate anus and tracheo-oesophageal fistula, and Sen's (1949) case also had an imperforate anus. Bowen's (1941) 12-year old patient was one of twins.

As far as I am aware this is the first case presented to this Society.

L.D.B., a female infant aged 7 weeks, was admitted on 18th June, 1958, as an emergency, to the surgical unit, with a history of vomiting of 3-days duration. This was attributed to an increase in her feed and was followed one day later by diarrhoea, the stools being at first brown and then green in colour with added slime. There was no recognizable blood in the motions. The vomiting persisted after every feed, the vomitus consisting of curdled milk only. The child had been fretful but was not screaming with pain. She had apparently passed urine frequently until the day prior to admission, when her mother noticed that she had wet her nappies less than usual. The abdomen had also become distended and hard.

On the day of admission the child appeared to be better, quiet and sleeping for periods. She was the fourth child of the family and had been delivered normally at home on the 26th April, 1958; birth weight 9 pounds. She was breast-fed for the first week and then weaned. There was no familial history of congenital anomalies.

On examination the temperature 99·2°, the pulse 130. The fontanelle was flat. The central nervous system, heart and lungs were normal. The weight was 11½ pounds. She lay quiet and at ease. The nutrition and colour were good. She did not appear dehydrated. The tongue was moist and clean; the nostrils, ears, pharynx, and lymph nodes normal. The abdomen was grossly distended by a large swelling rising upwards from the pelvis to the hypogastrium chiefly on the left side. There was some prominence of the superficial abdominal veins. The mass was tender, dull to percussion and firm in the upper pole. The lower pole lay in the pelvis and could be palpated by the rectal finger, lying anterior to the bowel wall. A provisional diagnosis was made of retention of urine with overflow. She was catheterized and 30 ounces of urine obtained after slow decompression. Paediatric advice was then sought, by which time 50 ounces of urine had been withdrawn. It was thought that she might have a gastro-enteritis, and a number of investigations were made. The urine was found to contain 200 mg. per cent of albumin, large numbers of pus cells, red blood corpuscles, and a culture growing *Escherichia coli* and an enterococcus.

Examination of the faeces showed nothing abnormal. The haemoglobin was 105 per cent, white blood cells 12,000 per c.mm. (polymorphs 24 per cent, lymphocytes 70 per cent, monocytes 4 per cent, eosinophils 2 per cent). An X-ray of the abdomen and chest, cystogram and I.V.P. were carried out, and it was only then that the true diagnosis was suspected, for the films showed an abdominal tumour arising from the pelvis, lying between the ureters, in front of the rectum and displacing the bladder upwards and to the left. The patient was then referred to the gynaecological department.

Examination confirmed the presence of an ovoid swelling extending upwards from the pelvis to about

2 fingers above the umbilicus. It was tense, cystic and fluctuant. To the left of the upper pole there was a firm irregularity. The rest of the abdomen was resonant. Inspection of the vulva disclosed a tense bulging membrane, just within the introitus with no evidence of a hymen; the membrane was not discoloured and was more marked when the child strained. The urethral orifice was normal. Rectally, the lower pole of the abdominal mass was found to extend downwards on the front of the rectum practically to the vulva. The anterior surface of the sacrum was regular. A diagnosis of hydrocolpos, originally made by the radiologist, seemed probable. The patient was taken to the theatre and a needle inserted through the centre of the membrane, 20 ml. of a greyish-brown turbid fluid being withdrawn. A similar amount of 25 per cent hypaque was injected and further X-rays taken. The following day under general anaesthesia the obstructing membrane was incised; 325 ml. of fluid similar to that obtained on aspiration being evacuated. The membrane was then completely excised, and pieces sent for histology, the pathological report reading as follows:

"The specimen consists of 2 white fragments up to 0·6 centimetres long, 2 of which at least are covered by squamous epithelium on both surfaces. The bulk of the tissue is fibrous with a few smooth muscle bundles. In one fragment there is an area of mild acute and chronic inflammatory infiltrate. In another there is a single tubule lined by a single layer of columnar epithelium—probably a portion of Gärtner's Duct."

The vaginal fluid was submitted to the bacteriologist who reported "a few polymorphs, many epithelial cells, occasional red blood cells. No growth on culture."

The child's subsequent progress was satisfactory, the urinary infection responding to sulphonamides. She was also given streptomycin and penicillin following the operation, and thereafter she passed urine normally, the abdomen becoming soft and flat. She was discharged on 10th July, 1958. On 26th November, 1958, her mother stated she was happy and content, her weight being 19 pounds 1½ ounces. There were no urinary difficulties and no vaginal discharge. The vulva appeared normal, and a probe passed for about 3 inches upwards into the vagina. Rectally, one could feel a small knob of tissue at the mid-line at the tip of the finger.

Discussion

The interest in this case lies in the importance of a hydrocolpos being kept in mind in the differential diagnosis of abdominal swellings occurring in female infants and the necessity in such cases of always inspecting the vulva. The obstructing membrane in hydrocolpos or haematocolpos seems to vary in its nature in different cases. The epithelium on the vulval aspect is generally squamous in type but on the closed side can be squamous, transitional or columnar. The membrane may also be situated at different levels. In the case described above it was indistinguishable from the hymen by the naked eye, but in Maliphant's (1948) and in Rea and Theron's (1957) patients it lay above the hymeneal fringe.

The level would appear to be determined by the degree of canalization on either side of the epithelial plate formed by the Müllerian tubercle above and the sino-vaginal bulbs below. The inconstant nature of the epithelium found on the superior surface of the membrane led Kanagasuntheram and Dassanayake (1958) to postulate a theory of plasticity or reversibility of embryonic epithelium, in support of which they quote the alteration of transitional to stratified squamous epithelium in the bladder in ectopia vesicae.

The fluid in hydrocolpos has been described variously as milky, like liquor, chyle-like, cloudy serous, turbid and yellow mucoid. The amount ranges from 1 dram (Spencer's case) in the neonates to 4 pints in a girl of 12 (Bowen's case). It has been found to contain epithelial cells, protein and sometimes glucose.

The source of the fluid was thoroughly investigated by Mahoney and Chamberlain (1940) in histological studies of the uterus, cervix and vagina, in specimens obtained at operation and post-mortem, in two infants respectively 3 weeks and 1 day old.

The striking feature they found was marked activity of the cervical glands—the uterus being slightly dilated and the vaginal epithelium thinned, compressed and keratinized—and concluded that they were the principal contributors to the secretion of fluid, the amount being determined by maternal oestrogen stimulation.

The fluid, however, does not resemble the normal sticky tenacious secretion of the adult cervix, and its origin must still be a matter for conjecture.

Summary

(1) Three cases of uterus didelphys with unilateral haematocolpos have been described in post-pubertal girls and one case of hydrocolpos in an infant.

(2) Attention is drawn to the importance of

suspecting gynatresia when pelvic swellings present in young female children.

(3) Treatment is simple and effective.

(4) The nature of the obstructing membrane and retained fluid in hydrocolpos is briefly discussed.

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THE ROUTINE USE OF THE ORIGINAL PFANNENSTIEL INCISION

BY

BRYAN WILLIAMS, M.D., F.R.C.S.E., F.R.C.O.G.
Middlesbrough Maternity Hospital

IN 1900 Pfannenstiel of Breslau described for pelvic surgery an incision in the lower abdomen cutting transversely the skin, superficial fascia and aponeurosis, with separation of the recti. Sometimes, however, his incision is described as being a transverse one through skin and superficial fascia only, followed by a vertical one through the aponeurosis, though this is more usually called a "modified Pfannenstiel incision". It is quite clear from the text and illustrations of his original article, that he advised a transverse incision through the aponeurosis. The other incision had previously been described by Rapin and Küstner, and Pfannenstiel considered that it protected "no more or no less" against incisional hernia than a mid-line one, and his object in introducing the incision now called after him was to prevent this complication while retaining the cosmetic advantages of the other incision. His incision might therefore be called a "modified Rapin-Küstner" incision, while the so-called "modified Pfannenstiel" should really be called the "Rapin-Küstner" incision. This latter incision combines the disadvantages of both incisions and need not be considered further. This recognition of what was really Pfannenstiel's original incision is important, as some surgeons have tried to improve on it by using an incision which Pfannenstiel himself gave up. Although in the title above, the term "original Pfannenstiel incision" has been used, it should now be sufficient to use the term "Pfannenstiel incision", and, after many years' confusion, it is time for us to appreciate that there is only one Pfannenstiel incision.

To any one who uses the original incision of Pfannenstiel regularly the advantages stand so high that it seems hardly necessary to explain them. The incision can be said to do much less harm to the structure and function of the abdominal wall than a mid-line one, as the wound tends to come together with muscle activity rather than to come apart. Sloan (1927) found that by attaching spring scales to the edges of both vertical and transverse incisions, the pull could be measured; it was thirty times as great on the vertical one. Recovery is therefore speeded, as early movement is not interfered with, and the risk of thrombosis and embolism is reduced. Full breathing is possible, especially as the wound is a long way from the ribs. Almost complete immunity is given from the risk of bursting of the abdomen or incisional hernia. Most of the incision lies near the site of operation. An excellent cosmetic result can be obtained. If spinal or epidural analgesia is used, a lower and safer level is all that is needed.

What are the disadvantages it is alleged to have? Inadequate exposure is said to be one of these, but this is not found if relaxation is adequate, and if the aponeurosis is separated well upwards and downwards, and the recti are well separated by sharp dissection. Opening of the abdomen may take longer, but surely this is not important, and, besides, closing of the abdomen can be quickly done. There may be more bleeding, but this is seldom serious. It is said that sepsis is more frequent, and this point will be discussed in dealing with technique. There are some minor disadvantages. Troublesome pain or discomfort at one extremity of the incision or in the groin may sometimes occur, and this may sometimes be due to picking up the ilio-inguinal nerve in the aponeurosis suture, and care must be taken to avoid this, especially on the left side. It is sometimes said that patients complain of numbness above the wound, and that they complain that they feel as if they have been "cut in half", but I think that these com-

plaints are rare, even when patients have been given full opportunity of mentioning any symptoms.

I believe that the advantages of the original incision as described by Pfannenstiel are so great, that it should be considered as the routine incision for gynaecological work and for Caesarean sections, unless there is some contra-indication, such as the following: the need for some haste, as in prolapse of the cord or ruptured ectopic pregnancy; the necessity for minimizing any blood loss; when there is doubt about the anaesthetic relaxation which may be forthcoming; where there is a large tumour, say one bigger than a 24-weeks pregnancy; when the whole abdomen has to be explored; and where there is already a vertical scar, not that there is usually any difficulty in separating the aponeurosis, but because rather unsightly cross-bow or anchor-shaped scarring results. These contra-indications are relative rather than absolute. Good exposure can be obtained if a long enough incision is made in the apeneurosis, and if the aponeurosis is well dissected upwards and downwards in the mid-line, and if the recti are well separated, and if the muscular relaxation provided by the anaesthetic is adequate. Pfannenstiel himself recognized the limitations of exposure, and did not recommend the incision for large tumours, or where extensive exploration is required as in malignancy.

There are a few technical points which I have found to be important. Unless care is taken it is easy to get an asymmetrical or sloping incision, especially at term, or when the abdomen is pendulous, or the umbilicus hidden with towels. It is advisable to determine carefully the position of the mid-line, and mark it with a scratch, and to make sure that the lateral ends of the incision have the same relationship to the anterior superior spines. The level of the incision can vary. Although Pfannenstiel described the skin incision as lying within the hair-bearing area, it is not necessary for a good cosmetic result for it to be as low as that, and indeed, if the incision is too low, much fibro-fatty tissue together with lymphatics have to be divided, the pyramidalis muscle may prove an embarrassment, and the incision in the aponeurosis may have to be V-shaped unless fibres are to be cut across. Usually about one-third of the way up from the pubes is a convenient level, and there is often a skin fold there. The anatomy of the pyramidalis muscles is very variable. It is best to dissect them off the aponeurosis, as recommended by Pfannenstiel, as otherwise there is troublesome bleeding and their blood supply is cut off. In these days when wound infection is so common, and sometimes so serious, it is important to avoid the contributing factors of collections of blood and serum, and to avoid making or leaving dead spaces. Bleeding should be carefully controlled, therefore, and the fat should not be too much dissected off the aponeurosis. The rectus should be brought together with a few interrupted catgut sutures, to prevent extra-peritoneal fat bulging between them and preventing healing, and at repeat operations a very sound mid-line is usually found. The use of tension sutures is unnecessary. The late Mr. Bryan Jeaffreson used continuous layers of smooth nylon in the skin, fat, and aponeurosis, coming out through the skin, and this technique avoids the irritant effects of buried catgut, and gives the good healing of a non-irritant non-absorbable suture, while avoiding the disadvantage of its being left behind. This technique gives excellent healing, but I have found some difficulty at times in removing the suture in the aponeurosis. Repeat operations through the scar present little difficulty, unless there has been a lot of sepsis, and indeed one is less likely to strike trouble than in going through the scar of a previous mid-line incision, with the chance of finding adherent small intestine not far under the skin. Not only is the abdominal wall sounder, but adhesions are less frequent.

Pfannenstiel considered that his method gave absolute protection against hernia. So far, I have seen no case in which either "bursting" of the abdomen or incisional hernia has occurred after a Pfannenstiel incision, but to review this matter further I have followed up and examined personally a series of cases operated on at least 2 years previously. There were altogether 79 patients, 44 of whom had had a gynaecological operation, and 35 Caesarean section. They were all unselected cases, either coming under observation for some other reason, or otherwise picked out at random. The only major compli

cation in the scar was one case of endometriosis following abdominal hysterotomy. In no case was any hernia found, even in one patient seen after 11 years, in whom it was necessary to insert packing through the abdominal wall at the time of operation to control bleeding from a myomectomy during pregnancy. In most cases the scar had stood up well both in appearance and strength to the passage of the years, or an obvious increase of weight. There was seldom any broadening of the scar or keloid formation.

I feel justified from my experience in assuring patients that it is "impossible" for them to "burst their stitches", and on one occasion when a patient insisted on going home 48 hours after a minor operation, I had no undue qualms. I feel that time has supported Pfannenstiel's claim that his incision has reduced the hazard of incisional hernia. Other reports (Hunter, 1940) show an almost complete absence of hernia formation.

The incidence of "burst abdomen" and ventral hernia, or both combined, sometimes described as "dehiscence", is variously estimated, but has been put as high as 7 per cent (Standeven, 1955), 10 per cent (Palumbo *et al.*, 1957) or even 12 per cent (Ross and Walsh, 1949). As with most other things, this figure will depend on what we call a "dehiscence" or on how hard we look for it, and of course on the types of operation included and the type of patient treated. It must be admitted, I fear, that gynaecologists have an unenviable reputation among their surgical colleagues for their incidence of ventral hernia, and it was once possible for Bland Sutton (1914) to say that bursting of the abdomen was more likely to follow Caesarean section than any other pelvic operation. With the present incidence of wound sepsis, it would seem that the incidence of burst abdomen may increase in spite of other improvements in surgical technique.

Cosmetic Result

A grudging place is sometimes accorded to this incision for the good cosmetic result which can be obtained with it, which is usually attributed to its being placed in the hair-bearing area. While it is true that Pfannenstiel himself did describe the skin incision as being in that area, I feel that in most cases it is impossible for an incision of adequate length to be entirely in the hair-bearing area, and that the good cosmetic result is due to the incision, even when much higher, being in Langer's line, or sometimes in a skin fold, and healing without keloid formation. A good result can be obtained by any careful method which brings together the superficial fascia, including Scarpa's fascia, and gives good skin apposition. I have now known many cases where the scar was overlooked, or found with difficulty, even with careful examination.

From time to time, other kinds of transverse incision have been described, such as those dividing the rectus partly or completely, or separating it from the pubes (Maylard, 1907; Cherney, 1941; Lees, 1953; Tollefson and Russell, 1954; Cohen, 1959), and while it is claimed that a transverse incision through all layers of the abdominal wall has many advantages, and gives very good exposure, and that the rectus can be cut with impunity, I think it goes against the instinct of most of us to cut the rectus, and the possibilities of harm are very great. Under the difficult conditions of war surgery in the Middle East, it was said (Ogilvie, 1946) that the surgeons who saw the late results of cutting the rectus "had never seen such herniae before, nor in their wildest nightmares dreamed them possible". Cutting the rectus should therefore, I feel, be only looked upon as an occasional emergency measure. Some of these authors show their reservations about cutting the rectus by saying that it may be sufficient to separate the muscles, and, though Cohen claims that pelvic surgery can be done without retractors in this way, I have found that, even without cutting the rectus, it is possible to dispense with self-retaining retractors, which I feel should now be of historical interest like the Trendelenburg position.

While there can be little dispute about the value of the Pfannenstiel incision for relatively minor operations, such as sterilization, it is in certain cases, where it proves more difficult in use, that its advantages are so great, e.g., in patients operated on late in labour, where the head is well engaged, and there is perhaps some degree of intra-partum infection. Such patients are very liable to develop abdominal distension

after delivery and get a "burst abdomen" if a mid-line incision is used. Patients with carcinoma of the body need early ambulation to avoid the risks from the commonly associated factors of age, obesity, hypertension and diabetes.

In one kind of case the Pfanennstiel incision is especially indicated: Mr. St. George Wilson (1936) used to point out the great risk of hernia occurring with a mid-line incision in patients operated on in pregnancy, where the pregnancy continued after operation. While a vertical incision may be advisable where the diagnosis is in doubt, the Pfannenstiel is preferable, when the diagnosis is fairly certain, e.g., an ovarian cyst complicating pregnancy and I have used it in such cases for very many years before I started using it as a routine in all other cases.

It is difficult for those of us who use this incision with enthusiasm to understand why it is not more generally used by experienced gynaecologists. Much of the opposition to it can only be based on inadequate experience with it, or on an incorrect understanding of what the Pfannenstiel incision really is. Even the standard textbooks of Operative Gynaecology in the English language, such as those of Wilfred Shaw (1954), Te Linde (1953), and Victor Bonney (1952), do not do adequate justice to it, in stating that it is only suitable for small operations, and that its only advantage is a cosmetic one. Thus Te Linde says he prefers the so-called "modified one", and Victor Bonney, after describing what appears to be the Küstner incision which Pfannenstiel gave up, says that its advantage is purely cosmetic, and he does not agree that there is less risk of scar hernia. He then goes on to describe the original Pfannenstiel incision, which he criticizes because he says that the advantage of the cosmetic results is lost.

Much of the opposition to this incision must date from the days when anaesthetic relaxation was less satisfactory than it is nowadays, and I must therefore acknowledge my debt to my anaesthetic colleagues, who, being convinced of the advantages of this incision to the patient, have been willing to co-operate in providing the necessary relaxation.

In my enthusiasm for this incision, I must also acknowledge my indebtedness to several distinguished Fellows of this Society, Mr. St. George Wilson, Mr. Percy Malpas, and the late Mr. Bryan Jeaffreson.

In the recently published *Obstetric and Gynecologic Milestones* by Speert (1958) there is a short biography of Pfannenstiel, together with a portrait, and translated extracts from his original article describing the incision. He was born in 1862, and after working at Breslau, from where he described his incision, he occupied chairs at Giessen and Kiel, and died at the age of 47 from a finger infection contracted while operating. With very great modesty, Pfannenstiel stated in his original article "Although the method provides other significant advantages, I do not wish to recommend it yet to my colleagues, for I am quite convinced that an ultimate verdict will only be possible after years". I submit that after 60 years it is now possible to give an emphatic verdict in favour of this incision, and that the best memorial to this great gynaecologist who gave his life for his work, would be for his incision to be well established and increasingly used in obstetrics and gynaecology.

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REPORTS OF SOCIETIES

NORTH OF ENGLAND OBSTETRICAL AND GYNAECOLOGICAL SOCIETY

MARCH 1960

A meeting of the North of England Obstetrical and Gynaecological Society was held in Sheffield on 18th March, 1960. The President, Professor T. N. A. Jeffcoate, was in the Chair.

Mr. C. R. Macdonald read a paper on

UNUSUAL FORMS OF GYNATRESIA

(This article appears on page 848 of this issue)

Discussion

The President thanked Mr. Macdonald for bringing these interesting cases before the Society. In the Liverpool museum there is a beautiful specimen of a double uterus and vagina removed in the days when the surgical approach was legitimate. In another patient Professor Jeffcoate had found a single haematocolpos and she had become pregnant first in the normal side and delivered normally, and then in the abnormal side and required a Caesarean section. The septum may have a tiny opening and infection gets in at childbirth producing a pyocolpos.

Mr. F. Stabler could hardly wait to mention his 15 cases in 12 of which there was a renal abnormality. One can often learn more from an incompetently conducted case. A girl of 14, whose grandmother had a double uterus, noticed a tarry discharge at the end of menstruation. It was thought that the right uterine horn was normal and the left was enlarged and that there was a single cervix. Later an offensive discharge was noticed, and the left uterine horn was removed. Despite this the discharge continued. She was then found to have a double vagina and a tiny bead of pus appeared at the little hole at the top where the septum is always thinnest.

Dr. W. Hunter had seen a similar case. There was a remarkable series reported in 1900 by B. H. Wells.

Mr. L. B. Patrick mentioned one case with unilateral pain and infection of the haematocolpos. The septum was excised.

Professor C. S. Russell showed a film

SIMPLE URETHROPLASTY FOR STRESS INCONTINENCE

The film was about the patient not operated on before who had stress incontinence and a cystourethrocele judged responsible for the urinary symptoms. In the operation an attempt is made to elevate and narrow the bladder neck in the simplest way. This corrects the visible fault, the narrowing takes up any slack in the involuntary sphincter, and the minimal surgery reduces the risk of devitalization, muscle atrophy or even fistula formation, for, out of 70 cases of fistula, 14 followed a repair. The operation is carried out at a rather more superficial level, so gaining a relatively avascular field and a thick layer of fascia superficial to the bladder.

Discussion

The President commented on the simple but effective approach for curing stress incontinence.

Mr. T. F. Redman used his finger to dissect into the cave of Retzius, but it was not always easy to see the different planes. He used catgut throughout.

Mr. J. M. King used non-absorbable sutures, but found later they have to be removed.

Dr. R. Newton found this operation the logical first step in the treatment of stress incontinence. He used catgut, and found if there was more bleeding there was more fibrosis and a better prognosis.

Mr. B. Williams described

THE ROUTINE USE OF A TRANSVERSE INCISION

(This article appears on page 853 of this issue)

Discussion

The President found he agreed with everything that had been said. At first he used it only on fat patients as access is better, but now he used it as a routine. Good relaxation was required. The incision was much more comfortable for the patient.

Mr. H. Agar took the opposite view for extensive gynaecological operations. He used a curved incision 1 inch above the inguinal ligaments, and in fat patients removed the redundant tissue.

Mr. Macdonald asked if another operation was done if the Pfannenstiel incision was repeated. He used continuous nylon for the sheath at first with no trouble, but there was infection with mersaline.

Mr. T. B. FitzGerald thought there was a limit to the amount of exposure as the upward flap cannot be extended.

Mr. D. H. Lees routinely used the transverse incision and showed a film. It did not give the exposure of the vertical incision and it takes longer.

Mr. P. Malpas thought the point of the Pfannenstiel incision was that an incisional hernia never occurred. It is not an incision to be made when the diagnosis is in doubt, and it is not suitable for fat women as infection

may be troublesome. Haematoma formation is common and the incision is best drained. He was impressed by the exposure when the recti were divided.

Mr. J. M. Gate wished to know if it was a suitable incision in very fat women.

In reply, Mr. Williams thought it fair to say most people were in favour of the incision. The incision should be curved, pressure was not needed, but the transverse incision should not be used if there was likely to be difficulty.

THE NUFFIELD FOUNDATION

MEDICAL FELLOWSHIPS

As part of its programme for the advancement of health, the Nuffield Foundation is prepared to award a number of fellowships to men and women of the United Kingdom highly qualified in medicine, usually between the ages of 25 and 35, who wish to train further for teaching and research appointments in any branch of medicine.

Applications for awards in 1961, which must first be endorsed by the executive authority of a university medical school in the United Kingdom, must be received by the Foundation not later than *1st February, 1961.*

The conditions of these fellowships and the application forms are obtainable from the Director, The Nuffield Foundation, Nuffield Lodge, Regent's Park, London, N.W.1.

L. FARRER-BROWN,
Director of the Nuffield Foundation

THE NUFFIELD FOUNDATION

NUFFIELD INSTITUTE FOR MEDICAL RESEARCH

RESEARCH FELLOWSHIPS

THE Nuffield Foundation, as an experiment, is prepared to offer one research fellowship in 1961, tenable at the Nuffield Institute for Medical Research at Oxford, to enable a suitably qualified person who intends to follow an academic career in obstetrics or paediatrics in the United Kingdom to concentrate for a year on animal experiments directly related to basic physiology or pharmacology in the foetus or the newborn.

Each fellowship will be tenable for one year and is limited to a graduate in medicine of a University within the British Commonwealth, who should either have completed an appointment as Registrar (or its equivalent) in an approved department of obstetrics or paediatrics, or be seconded for one year from such an appointment. He should also have obtained the higher qualification appropriate to his chosen speciality. The stipend will be within the approved range of salaries for Senior Registrars under the National Health Service. Applications for the award beginning in 1961 must be received before 15th February, 1961, by the Director, The Nuffield Foundation, Nuffield Lodge, Regent's Park, N.W.1, from whom full particulars and application forms can be obtained.

L. FARRER-BROWN,
Director of the Nuffield Foundation

HOSPITAL REPORTS

BY

J. S. TOMKINSON, M.B., F.R.C.S., M.R.C.O.G.

THE MATERNITY REPORT OF KING'S COLLEGE HOSPITAL FOR 1957

THE recommendations of the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists are followed in this report. Table I is divided into (*a*) Associated Diseases (excluding diabetes) and (*b*) Associated Diseases (Pregnancy and Diabetes). In this way the large number of diabetic patients treated in the obstetric department at King's College Hospital are analyzed separately. During the year, 583 patients were delivered, without a maternal death. The stillbirth rate was 22·1 per 1,000 total births and the neonatal death rate was 9·52 per 1,000 live births. An interesting comparative table of statistics for 9 years is included and this indicates that, whilst the stillbirth rate remained fairly constant, the neonatal death rate was the lowest in the 9 years reviewed. The forceps delivery rate, at 8·2 per cent, was also the lowest during the same time, whilst the Caesarean section rate, at 10·6 per cent, was the highest.

The results obtained in patients who were pregnant with diabetes are summarized in the report as:

Pregnancy associated with Diabetes:

	Cases
Spontaneous abortion	43
Therapeutic termination prior to 28 weeks	3
Induction of labour (includes 1 patient who subsequently had a L.S.C.S.)	11
Spontaneous onset of labour (includes 1 patient who subsequently had a L.S.C.S.)	5
L.S.C.S.	22
Stillbirths	4=11·1%
Neonatal deaths	3=8·35%
Total foetal loss	=19·4%

The treatment of the pregnant diabetic patient in 1957 was:

(*a*) Strict control of maternal diabetes. Patients attend the diabetic clinic on the same day that they attend the antenatal clinic. Diabetic treatment is supervised by Dr. W. G. Oakley.

(*b*) Admission for rest and stabilization of the diabetes at 32 weeks. The patients then remain in hospital until after delivery. In many cases this admission has only been possible by the generous "loan" by Dr. Oakley of beds in the Diabetic Wing.

(*c*) Delivery at or about 36–37 weeks. In the case of primigravidae this is accomplished by set L.S.C.S. Multigravidae who have had a previous successful vaginal delivery are induced by rupture of the membranes.

(*d*) Care of the newborn infant (after any initial resuscitation) is supervised by Dr. Mary J. Wilmers.

THE MATERNITY REPORT OF KING'S COLLEGE HOSPITAL FOR 1958

THIS follows closely the report for 1957 (see above). Additional tables are included for "Rhesus antibodies" and "Shirodker's operation" (one hopes that the spelling will be corrected in subsequent reports). The valuable table of comparative statistics is continued and now 10-years results may be seen at a glance. In 1958, the maternity department delivered 935 patients, with 3 maternal deaths (due to (*i*) cerebral haemorrhage, (*ii*) respiratory failure and sickle cell anaemia, (*iii*) pulmonary embolus on the 12th day of the puerperium). The stillbirth rate was 21·9 per 1,000 total births and the neonatal death rate was 17·7 per 1,000 live births. The incidence of forceps delivery and Caesarean section was 13·4 per cent and 10·5 per cent respectively.

No alteration in the treatment of pregnancy with diabetes is recorded from that given in the 1957 report. The results in this condition were:

	Cases
Pregnancy associated with Diabetes ..	47
Spontaneous abortion	1
Therapeutic termination prior to 28 weeks induction of labour (includes 4 patients who subsequently had L.S.C.S.)	6
Spontaneous onset of labour ..	4
L.S.C.S.	26
Stillbirths	3= 6·3%
Neonatal deaths	6=12·7%
Total foetal loss	9=19%

NATIONAL MATERNITY HOSPITAL, DUBLIN, CLINICAL REPORT FOR 1958

THE annual reports from this hospital are always well produced and full of interest; the report for 1958 is thoroughly up to standard. The summary of the intern

department's activities gives an excellent statistical analysis of the work done. With 138 beds, 4,474 mothers were delivered, two-thirds being booked cases. Nine cases of maternal mortality occurred. The Clinical Report is presented by the Master, Dr. Charles F. V. Coyle. He mentions the changes in staffing and gives an overall picture of the work of the hospital during the year. With a bed occupancy of 99·7 per cent a plea is made for more beds. There follows a commentary, by the Master, of each of the Tables of obstetrical conditions which is a most valuable contribution and which could be adopted by other hospital reports for the benefit of those outside the hospital. The usual management of a condition can be outlined, any improvements in technique mentioned and any unusual features of the cases brought out and enlivened, instead of a bare presentation of rows of figures.

The report indicates that a wide range of obstetric complications were encountered during the year, 16 cases of face presentation, 10 of brow presentation, 20 of transverse lie and 35 of presentation and prolapse of the cord. The forceps delivery rate was 11·7 per cent (a slight increase on 1957) of the total of 471 cases; in 252 the indication was failure to advance in the second stage of labour, in 91 the indication was foetal distress and in 128 maternal distress. Symphysiotomy was performed 6 times, in 2 cases "on the way out" from Caesarean section and once as an elective procedure in a patient who had lost her previous 2 babies and who had had a previous Caesarean section. A vaginal delivery following previous symphysiotomy occurred in 30 cases, 2 requiring a forceps delivery and the remainder being spontaneous deliveries. The Caesarean section rate was 2·2 per cent of all deliveries over 28 weeks gestation on the intern service.

Rupture of the uterus was encountered 7 times; in 4 the rupture was spontaneous (in one instance there had been a previous lower segment Caesarean section), in 2 an oxytocin infusion had been used and in the remaining case the uterus was damaged during a difficult breech extraction.

One case of "c" iso-immunization occurred in 70 cases of haemolytic disease of the newborn; the total foetal loss being 25 (3 abortions, 14 stillbirths and 8 neonatal deaths). The hospital is to be congratulated on the results of diabetic pregnancies; of the 19 intern cases there were only 2 neonatal deaths, a survival rate of 89·5 per cent.

An immense amount of work has gone into the production of this report and it has been worth the effort. One is happy to recommend it whole-heartedly.

THE ROYAL MATERNITY HOSPITAL, BELFAST, ANNUAL REPORT FOR 1957

This report consists of the tables recommended by the Standard Maternity Hospital Report Committee of the Royal College. There is no introductory preface to indicate whether there is any selection in patients admitted for delivery, no mention of the number of beds available, no index and no analysis of results obtained. So it is rather an effort to review this report; for instance, a page by page search has been made to find out the number of patients delivered during the year but the information cannot be found and so no calculations can be made to discover the incidence of various conditions, complications and procedures. Five maternal deaths occurred in 1957 which indicates that probably several thousand patients were in fact delivered. The paediatric summary states that the total births was 2,037, but of course this is not necessarily equal to the number of patients delivered.

A report such as this is nearly valueless unless a few basic facts are included. Your reviewer has been defeated.

THE SOUTHMEAD GENERAL HOSPITAL, DEPARTMENT OF OBSTETRICS (B BLOCK) REPORT FOR 1957

This hospital has two separate units in its Maternity Department, one block being the Professorial Unit, the other block (of which this is an annual report) being designated B block and functioning independently. During 1957 there were 2,177 deliveries, of which 380 (19 per cent) were emergency admissions from other maternity hospitals and cases from the counties of Somerset, Gloucester and also from Bristol. One maternal death occurred; the stillbirth rate was 40·8 per 1,000 total births and the neonatal death rate was 22·8 per 1,000 live births. The Caesarean section incidence was 7·7 per cent and the forceps delivery incidence 10·0 per cent.

Twenty per cent of all cases were surgically induced, a total of 450 patients; the indication for induction in 225 was toxaemia and, in 116, postmaturity. Of those patients surgically induced, a Caesarean section was performed in 6·45 per cent.

The report consists of summaries of the tables recommended by the Standard Maternity Hospital Report Committee. There is no index and no table of comparative statistics for previous years.

THE SOUTHMEAD GENERAL HOSPITAL, DEPARTMENT OF OBSTETRICS (B BLOCK) REPORT FOR 1958

This report is for the same unit as that reviewed above. Presumably similar emergency admissions were received in the department as in 1957, but there is no preface in the report for 1958 to indicate this. The total deliveries were 2,085, no maternal death occurred, the stillbirth rate was 36·3 per 1,000 total births and the neonatal death rate 23·9 per 1,000 live births. The Caesarean section incidence was 5 per cent. The forceps delivery rate in this year rose to 18 per cent and the number of patients surgically induced was 815 (40 per cent of all deliveries, being double that of the same department in 1957). A Caesarean section was performed in 32 patients surgically induced, an incidence of 3·5 per cent, nearly half that of the previous year.

In 1958, the number of patients induced for toxaemia and hypertension was 449 (double the number induced for the same condition in 1957). The foetal loss was 12 in the 449 patients so induced; it is not possible to compare this result with the preceding year as comparable figures were not given. There is no index for this report.

THE BOARD OF MANAGEMENT FOR GLASGOW ROYAL INFIRMARY AND ASSOCIATED HOSPITALS; THE EASTERN DISTRICT HOSPITAL MATERNITY UNIT ANNUAL REPORTS FOR 1952–1956

THIS is a short and interesting report covering 5 years; it is well produced and could well be taken as a model for those hospitals wishing to save themselves the expense and time involved in publishing the usual type of maternity hospital report.

A comprehensive statistical summary for the 5 years is given, followed by summaries of the tables recommended by the Standard Maternity Hospital Report Committee of the Royal College. At a glance, any page of the report will show the variation from year to year of the incidence of any condition and of any complication, how it was treated and the results obtained. The tables for surgical induction of labour (Table 25) and Caesarean section (Table 26) show how interesting this comparative method is.

This maternity unit delivers about 1,300 patients a year. The number of beds available is not mentioned, nor is there any indication as to whether there is any selection in the kind of patients booked for delivery. Three maternal deaths occurred in the 5 years. The stillbirth rate varied from 25·81 to 37·03 per 1,000 live and stillbirths and the neonatal death rate from 21·98 to 31·76 per 1,000 live births. The forceps delivery incidence was between 7 and 10 per cent, the Caesarean section rate varied from 3·8 per cent to 5·91 per cent and about 10 per cent of all patients were surgically induced.

In its thirty-one pages this report includes detailed notes on the maternal deaths, maternal cases of special interest, a short paediatric report and paediatric cases of special interest. This is a very worthwhile report.

AREA DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, UNITED OXFORD HOSPITALS; ANNUAL REPORT 1959

THIS report is produced and distributed with commendable promptitude for a copy was sent for review a few months after the end of the year. It consists of sheets of typescript loosely clipped together; the material of the report is in the form of statistical analyses of the work done by the several units of the Area Department, followed by the results of a few procedures or complications, such as surgical induction of labour, placenta praevia, erythroblastosis foetalis, stillbirths, neonatal deaths and premature babies. Three thousand four hundred and eight patients were delivered, with a stillbirth rate of 17·1 per 1,000 total births, a neonatal death rate of 15·0 per 1,000 live births, a Caesarean section rate of 4·4 per cent and a forceps delivery rate of 15·8 per cent. One maternal death occurred from collapse due to a pulmonary embolus, 30 minutes after a Caesarean section (continuous spinal analgesia) for fulminating pre-eclampsia at the 26th week of pregnancy in a primigravida aged 30.

A gynaecological report is included. The department is renowned for the expertness of its vaginal hysterectomies and this is reflected in the frequency with which this operation is performed—295 vaginal hysterectomies, 254 total abdominal hysterectomies and 92 pelvic floor repairs. Eight patients died from malignant gynaecological lesions. The report closes with an interesting account of the activities and successes of the members of the department.

KINGSTON HOSPITAL, OBSTETRIC DEPARTMENT, CLINICAL REPORT FOR THE YEAR ENDING 31ST AUGUST, 1958

THE preface to the report states that this is the first Clinical Report to be published by this department. It follows the 1948 recommendations of the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists. The department had 17 antenatal and 74 lying-in beds, but for part of the year about 20 beds could not be used as structural alterations were in progress. A premature baby unit and beds available for general practitioners are included in the department. There were 1,718 patients delivered in the hospital in 1958, nearly equally divided into primigravidae and multigravidae. One maternal death occurred, a case of virus encephalitis at the 28th week of pregnancy simulating eclampsia and requiring a tracheotomy and assisted respiration. A note is made of a patient who recovered after an acute inversion of the uterus. The stillbirth rate was 19·5 per 1,000 total births and the neonatal death rate 12·3 per 1,000 live births. The forceps delivery rate was 11 per cent and the incidence of Caesarean section 2·4 per cent. An external version before labour was attempted in 79 cases and failed in only 4 instances, an anaesthetic was given to 4 patients and a successful version performed; there was no foetal loss.

The department is congratulated for the excellence of its first report. Perhaps an index could be put in successive issues and, as time goes on, the statistical summary made into a table of comparative results for each year.

OUR LADY OF LOURDES HOSPITAL, DROGHEDA, CO. LOUTH, IRELAND, CLINICAL REPORT FOR 1958

THIS is a well set out report from a hospital which delivered 1,309 mothers after the 28th week of pregnancy, of which a quarter were primigravidae. There were 65 beds available. The recommendations of the Standard

Maternity Hospital Report Committee are followed for the main part; some of the tables are summarized and this has given an opportunity for a short explanatory description to be given of the management of a condition or procedure. There is a statistical summary of the work done and the results achieved and also a rather more detailed analysis of the intern service. One maternal death occurred 90 minutes after delivery, from bronchopneumonia, in a primigravida aged 42 who had had gross hydramnios, a forceps delivery of a macerated anencephalic foetus at term (under inhalation anaesthesia) and then a manual removal of the placenta (under intravenous and inhalation anaesthesia).

The stillbirth rate in 1958 was 31 per 1,000 total births and the neonatal death rate 16 per 1,000 live births. The Caesarean section rate was 3·3 per cent and that for forceps delivery 11·5 per cent. Symphysiotomy was performed in 21 patients with disproportion, without maternal or foetal loss; in 2 of these patients a Caesarean section was necessary, due to inertia and both have since had a spontaneous vaginal delivery. Eighteen patients had a vaginal delivery following a previous symphysiotomy.

Four cases of unusual interest are recorded; these were a case of subarachnoid haemorrhage (mother and child surviving), a carcinoma of cervix presenting as antepartum haemorrhage and 2 cases of rupture of the uterus. The last 2 patients were both para-6; in one the uterus tore along the left side after the fifth injection of pitocin for induction of labour, in the other the tear was in the lower segment of the uterus after spontaneous onset of labour; hysterectomy was performed in both instances with successful recovery. One baby was lost.

This hospital, which is an International Missionary Training Centre, is congratulated on the excellence of its annual report.

THE MATERNITY REPORT OF THE WOOLWICH GROUP HOSPITAL MANAGEMENT COMMITTEE FOR 1957

THIS report is a composite one for the five hospitals comprising the Woolwich Group. The hospitals are the British Hospital for Mothers and Babies (1,405 deliveries), War Memorial Hospital, Woolwich (310 deliveries), Bexley Maternity Hospital (660 deliveries), Russell Stoneham Maternity Hospital (585 deliveries) and the Hainault Maternity Hospital (449 deliveries). The report is a summarization of the tables recommended by the Standard Maternity Hospital Committee, making for "easy reference, and appreciation of significant relationships".

A useful table of comparative statistics reviews the results of 1957 with those of the previous 7 years. The maternal mortality rate of 0·29 per 1,000 live and stillbirths was less than half the national figures for 1956 and the stillbirth and neonatal death rates were also below the national averages. The Caesarean section rate for the eight years is 1·55 per cent. The forceps delivery rate was 7 per cent in 1957.

FOOTSCRAY AND DISTRICT HOSPITAL, MATERNITY MEDICAL REPORT FOR 1957

AT first it was a puzzle to know whence this report came; the only Footscray that came to mind was in Kent, England. Then a perusal of the list of consultants gave a clue—it must be in or near Melbourne, Victoria, Australia. This hospital, with 25 public obstetric beds, delivered 1,045 patients during the year. The stillbirth rate was 13·9 per 1,000 total births and the neonatal death rate 10·4 per 1,000 live births. One maternal death occurred from a ruptured aortic aneurysm, the patient collapsing the day after she had been delivered by low forceps; she was 21 years old and a primigravida.

A surgical induction of labour was performed in 88 cases. The indication was postmaturity in 30 patients and toxaemia and hypertension in 52; Caesarean section was necessary twice. Medical induction of labour is tabled separately; it was carried out in 35 patients, using "Pitocin" intramuscularly or intravenously or "Pituitrin" intramuscularly with the loss of 2 infants (one tentorial tear and one intra-uterine death at the 28th week of pregnancy with a concealed ante-partum haemorrhage); one Caesarean section was necessary in this group of patients and 11 failed to deliver in 96 hours. A Caesarean section was performed in 45 patients, a rate of 4·3 per cent; all were lower segment incisions except for 2 classical sections for transverse lie. The forceps delivery rate was 7·1 per cent.

Two cases of special interest are described; one being a multiple pregnancy occurring after a subtotal hysterectomy which is worth quoting in full from the report:

Mrs. M., aged 33 years, presented to Gynae. O.P. on 15th August, 1957, with increasing abdominal tumour which she had noticed for six months.

Her previous obstetric history at another hospital was as follows:

"Classical Caesarean section 1945 following trial of labour. In 1956 she had a rupture of the uterus with a 26-week twin pregnancy. This was diagnosed following onset of acute abdominal pain and fainting. She was given blood and laparotomy was performed.

"The lower end of the classical C.S. scar had ruptured, with both sacs protruding through the rupture.

"Subtotal hysterectomy was performed. It was noted that the right tube and ovary and round ligament were absent, but it was not practical to explore the pelvis further.

"The tumour, on 15.8.57, was thought to be an ovarian cystadenoma. An X-ray, however, showed the presence of twin foetuses—development approximately 26 weeks.

"Four days later, following onset of suprapubic pain, the patient aborted one foetus at home. The sex was unknown.

"She was admitted and sedated. Two days later the second foetus, a living female, was aborted. Curettage, at which a double placenta was removed, was necessary for completion of the third stage."

This is an interesting report and the hospital is congratulated on the excellence of its results.

ST. LUKE'S HOSPITAL, ANUA, UYO, EASTERN NIGERIA. THE 11TH ANNUAL REPORT FROM DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, 1957

THIS is a precise and well produced report, following the recommendations of the Standard Maternity Hospital Report Committee of the Royal College of Obstetricians and Gynaecologists. The hospital had 50 obstetric beds and 30 gynaecological beds in 1957. Six hundred and seventy patients were delivered, 580 being booked cases. In addition, 569 patients were delivered by the extern department. The high standard of obstetrics achieved is vividly shown by the difference in maternal mortality between booked and unbooked cases; there was no maternal death in the booked, but a maternal mortality rate of 77 per 1,000 in the unbooked. The tragic condition of these patients is well described in a note on maternal mortality which is quoted in full:

"*Note on Maternal Mortality. Number of Cases, 7. Percentage, 1·5*

"As will be noted all these obstetric tragedies were in Unbooked Cases. And in this connection it is unbooked in the strict meaning of the term. Not only did they have no antenatal care but they in their ignorance consulted the native bush doctor. The condition of these patients on admission to hospital has to be seen to be believed.

"The patient after her experiences at the hands of the unqualified quack presents a tense anxious appearance. Her vulva is oedematous and tender, her uterus is usually in tonic contraction after the native oxytocic drugs which have the same action as pitocin, and are administered generously during the last month of pregnancy with often disastrous results, especially if the patient is a multipara. Most often these cases are primigravidae, young, and very eager to bear their first child for their husband's sake as well as their own. The husband on his part has very little say as regards his young wife's first confinement. His mother-in-law looks into that and if the native doctor was good enough for her she should deliver her daughter. This for us doctors in the tropics is a very sad duty to deliver these mothers of dead babies and then in spite of every modern drug, blood transfusion, etc., see them die. This may give European readers of this report the social and cultural background of a 77·7 per thousand maternal mortality in unbooked cases.

"Our maternal mortality in booked cases for 1957 is the more consoling figure of 0."

Symphysiotomy was used in 77 cases; there was a gross foetal loss of 13 infants, this being due to the particular type of case operated on rather than due to the operation. The Caesarean section rate was 5·3 per cent, all were performed under local anaesthesia and all were the lower segment type of operation. The forceps delivery rate was 2·3 per cent.

BOOK REVIEWS

"Fluid Balance in Obstetrics: A Critical Review." By PHILIP RHODES, F.R.C.S., M.R.C.O.G. Pp. x+165. Lloyd-Luke, London, 1960. Price 25*s*.

THIS book is a brave attempt at a difficult subject. The difficulties lie in our present lack of exact knowledge of relevant physiology and pathology, and therefore those aspects of fluid balance in obstetrics of which we know relatively more are dealt with more easily and more convincingly. This is probably why the chapter on anuria and oliguria is the most satisfying to the reader. For the rest, the gaps in our knowledge are many, and it is doubtful how far the author's manifest delight in mathematical calculations helps to explain discrepancies between the theoretical considerations and the practical observations of others. This is not to disparage a praiseworthy effort to put the subject on a more rational basis than it is usually afforded in practice. The lines along which further research is likely to be most fruitful are suggested, for instance in pre-eclampsia where cell membrane permeability and the factors controlling it are held to offer the key to solving the problems of toxaemia. Altogether, this is a book which is a reminder of what we still have to discover rather than a collation of what we already know, and therefore stimulating rather than satisfying.

S. Bender

"Congenital Malformations, a Symposium." Edited by G. E. W. WOLSTENHOLME and CECILIA M. O'CONNOR. Pp. xii+308, with 91 illustrations. Churchill, London, 1960. Price 45*s*.

THE editors and publishers are to be congratulated on making this Ciba Foundation Symposium of January, 1960 available in book form within 6 months. Many of the speakers, both from Britain and overseas, also participated in the more recent First International Conference on Congenital Malformations held, also in London, in July, 1960. The 12 papers and related discussions which comprise this book range over a wide field of natural and experimental teratogenesis. The lay press recently deplored our ignorance in this sphere; this book makes it clear what an enormous amount of knowledge has been obtained in the relatively short time over which this enormous and many-sided subject has been intensively studied. The papers of particular interest to the practising obstetrician are those on anencephaly (A. Giroud) and on the association of hydramnios with congenital malformations (A. C. Stevenson); while experiments with teratogenic agents may point to the possibility of their eventual use to procure therapeutic abortion.

"Mitra Operation for Cancer of the Cervix." By SUBODH MITRA. Pp. 93, with 38 figures. Blackwell Scientific Publications, Oxford, 1960. Price 48*s*.

THIS book will be of real interest to all those who are concerned with the treatment of cancer of the cervix. For many years Dr. Mitra has been an exponent of the Schauta operation for cervical cancer. Between 1932 and 1950 he performed this operation on 209 cases of cervical cancer, out of 1,276 cases seen, with a primary mortality of 2·8 per cent. He now reports on 216 cases in which he has extended the operation, and the new technique consists of a bilateral extra-peritoneal dissection of the pelvic lymph nodes through two separate oblique abdominal incisions, followed on the same occasion by a Schauta excision of the uterus and parametria. The operative mortality was 3·6 per cent (although 3·6 per cent of 216 patients works out at 7·7 deaths; presumably the figure relates to the 194 cases that he operated on himself). He claims that this procedure is preferable to Wertheim's operation.

Unfortunately he does not state his operability rate. For the preceding Schauta series the rate was 16·4 per cent (not 17 per cent as stated) of all cases seen, or 28 per cent of cases in Stages I and II. The argument in the text that this rate ought to be, or could be, 45 per cent seems a little unreal, although it may well be that there are difficulties over consent for operation in some of these cases.

The primary problem of the choice between surgery and radiotherapy is almost ignored. Dr. Mitra was disappointed with the results of radiotherapy in 1931, and so turned to surgical treatment. The only subsequent comparison that he offers is for the years 1950–1951, in which surgical treatment gave a five-year survival rate for cases in Stages I and II of 66 per cent, whereas radiotherapy gave a rate of 47 per cent. But if we grant his choice of surgical treatment, towards which the reviewer must confess to some bias, then we must ask whether the new procedure is superior to Schauta's operation, or to the modern type of Wertheim operation in which the lymph nodes are removed as a routine. The author compares 33 Schauta operations with 35 of the new operations (1943–1952); the five-year survival rates were 45 per cent and 61 per cent, though the numbers are small, and the table does not give the proportion of the cases in the different stages. Elsewhere he shows that he was able to save 4 out of 15 cases with involved nodes, so that the extension of Schauta's operation would seem to improve the results.

However, the comparison of the Mitra operation with the modern modifications of Wertheim's operation is less easy. Presumably the excision of the lymph nodes is

equally effective by either method, so the argument in favour of the new procedure must rest on the operative risk and the extent of parametrium removed. It may be that Dr. Mitra has to deal with some patients whose nutrition and general health are poor, and his primary mortality, and the fact that he only had two fistulae in this series are testimonials to his skill. Yet the argument that it is safer to perform this operation than the Wertheim operation is to be questioned, especially when comparing these results with those who have had a large experience of Wertheim's operation, such as Currie of Leeds.

It is of great interest that Dr. Mitra found microscopical evidence of parametrial involvement in only 32 out of 216 cases, although there was such involvement in 13 out of 114 cases in clinical stage I. His statement that, "whatever the clinical staging, one is not justified in limiting the surgery in any stage of cancer of the cervix except in stage O" will have support.

The final judgment on any operation for cancer must rest on the five-year survival rate, and this was 61 per cent (1943–1953), with a rate of 64 per cent for cases in Stages I and II. Whether other surgeons agree with this choice of operative procedure or not, they will study these results with interest, and congratulate the author on his enthusiasm and hard work.

Turning now to consider this monograph as a book, the reviewer is less happy. Its price is high, and the drawings of the operation are poor; indeed some of them would mean very little to anyone who had not seen the Schauta operation performed.

"Electrohysterography." By S. D. LARKS, Assistant Professor of Biophysics in the University of California. Pp. 123, with 43 figures. Blackwell Scientific Publications, Oxford, 1960. Price 46*s*.

THIS is a useful monograph, embodying information from many sources, some of which are not otherwise easily accessible. Readers of the Journal will remember an article on Pacemaker Function in the Uterus by the author and his colleagues (1959, **66**, 229), and this book amplifies the facts and theories that were there presented.

There is an interesting historical review of the early discoveries and theories about "animal electricity", and the survey passes on from Galvani and Volta to Einthoven and the electrocardiograph. The bioelectric changes that occur in muscle are fully discussed, and, although the mathematical formulae in this section will probably be incomprehensible to most doctors (and certainly were to your reviewer), this is a small difficulty, for the conclusions reached are explained in more simple terms. Details of technique are included, with descriptions of the apparatus used, and of such practical matters as the preparation of the skin and application of the electrodes.

Dr. Larks produces good evidence from his electrohysterographs to show that the right cornu of the uterus acts as a pacemaker, and that most normal contractions originate there. His discussion of abnormal labour is less satisfactory, both as regards the terms used and the number of observations made. (Figure 19 seems a bit overworked; it appears again as Figure 29 and later as Figure 34.) The author would probably agree that this research has only just passed the initial stage, and we may now hope for further studies of abnormal labour from him and from others. Knowledge of this new technique, and training of personnel who have the necessary ability in mathematics and physics, may lead to great advances in our knowledge of uterine action, just as the electrocardiograph did in cardiology.

The book is elegantly printed and produced, but it does seem expensive for its size.

"Sex Differentiation and Development." Edited by C. R. AUSTIN. Pp. 193, illustrations. Cambridge University Press, London, 1960. Price 45*s*.

FASCINATING in content and wide in range, the latest Memoir of the Society for Endocrinology maintains the very high standard of its predecessors. The proceedings of the symposium held in London in April, 1958 which are herein reported covered mechanisms of sex determination, differentiation of germ cells, manifestations of sex, and sexual anomalies. From consideration of sexuality in bacteria to descriptions of human intersex syndromes, a wide field of past experiment, present research and future prospects (some of which have been attained since the time of the conference) is set forth. In this book is the common meeting-ground of zoologist, biologist, physiologist, endocrinologist and gynaecologist. The last will be particularly interested in the discussions on the possibility of controlling the sex ratio at conception, and in the papers on sex chromatin, sex reversal and intersex states.

"Family Planning." By J. F. ROBINSON. Pp. 64, with 15 figures. E. & S. Livingstone, Edinburgh and London, 1960. Price 3*s*. 6*d*.

DR. ROBINSON, a Leeds general practitioner, has already to his credit the authorship of *Having a Baby*, a small and sensible book for young married couples. *Family Planning* is a short reasoned and practical account of another marital problem. Contraception is the main text, but the author emphasizes that it is important for a couple to prove their fertility fairly early in married life, and that the pleasures of a family are often not realized until after a baby has been born.

"Handbook of Haematological and Blood Transfusion Technique." By J. W. DELANEY, F.I.M.L.T. Pp. 311, illustrations. Butterworths, London, 1960. Price 45*s*.

THIS comprehensive handbook is designed primarily for the laboratory technician in training and practice, but as it covers much basic physiology and pathology it will be useful reading for the medical student and the hospital resident too.

"Recommendations of the International Commission on Radiological Protection." Report of Committee II on Permissible Dose for Internal Radiation. Pp.

xxxii+233. Permagon Press, London, 1959. Price 30*s*.

THE task of Committee II of the International Commission on Radiological Protection is to recommend values of the maximum amounts of radioactive material which may be tolerated within the body without risk of somatic or genetic damage and also the maximum concentration of these substances which may be safely tolerated in water and food. The recommendations which are now published apply to three groups of persons: those whose occupation exposes them continuously to radiation from the various kinds of isotopes, those who have occasional exposure to radiation in the course of their daily duties, and the population at large.

A great deal of useful technical data has been assembled by the Committee, and the permissible doses quoted and the recommendations which they have made are based on the best information which is available at present on the concentration and excretion of each isotope. As further knowledge accumulates, alterations will undoubtedly have to be made from time to time.

The book is an essential reference manual for those who are concerned with the health and safety of radiation workers and with the hazards to the general population from radioactive isotopes.

Robert Morrison

"Fortschritte der Geburtshilfe und Gynäkologie." Vol. 10. Edited by A. REIST. "Das neurovegetative Nervensystem" (The Autonomic Nervous System). With contributions by J. ARTNER and G. A. HAUSER. Pp. vi+258, with 98 figures. S. Karger, Basel and New York, 1960. Price Sw.Fr. 32.

THE two contributions included in this volume deal with the changes in the autonomic nervous system during the menstrual cycle and with their significance in the hormonal control of sexual function. The second of the two contributions (242 pages) is the more important. In it Dr. Hauser records the results of his detailed examination of 800 patients, attending the University Gynaecological Clinic, Basel, who complained of a variety of so-called functional disorders. By careful history-taking and using a battery of special investigations he has attempted to classify the disorders of function of the sympathetic and parasympathetic nervous systems and imbalance between these two systems in relation to the various functional disorders of the female genital tract, including the syndrome of pre-menstrual tension, metropathia haemorrhagica, the climacteric, etc. The tests used to elucidate the nature of autonomic function in each patient included, the adrenaline test (Sturm), the cold-pressor test (Hines and Brown), the orthostatic test of Schellong, the warming-up test of Ibsen, the measurement of the electrical resistance of the skin, the injection of pyrogen, the redoxtest (Meier and Synek), and, the measurement of the triple skin response (dermatographismus).

Dr. Hauser has made a valuable contribution to our knowledge with this monograph; besides his detailed and careful observations in a wide variety of gynaecological disorders, he has summarized the literature on the subject and reviewed the present state of our knowledge with regard to the anatomy and physiology of the autonomic supply of the female generative organs. There is also a useful chapter on the role of the autonomic system in pregnancy and labour. The list of 834 references gives some idea of the scope of the work. The value of the results of the research published here is not in the discovery of new facts, but in the painstaking and exemplary way that the author has attempted to unravel and understand, in their widest sense, the disorders of gynaecological function.

Peter J. Huntingford

"Typical Gynecologic Operations." By SIEGFRIED TAPFER, M.D. Translated by L. M. Szamek, M.D., from the 2nd German Edition. Pp. 81 with 168 plates. J. B. Lippincott, Philadelphia, and Pitman Medical Publishing Co. Ltd., London. Price 72*s*.

THE author from his long experience of operative technique in the Austrian Schools, describes succintly the operations of Supravaginal Hysterectomy, Total Hysterectomy, Wertheim's Hysterectomy, Pelvic Floor Repair, Vaginal Hysterectomy, Schauta Hysterectomy and Radical Vulvectomy. The descriptions are clear and the translation nearly always good. There are no photographs, all the 168 plates being drawings by Dr. Wenzel. They illustrate very clearly the anatomy and the steps of the operations. The description and drawings of the Schauta-Amreich operation are particularly lucid. In general, the techniques shown are the standard practice in Austria.

This is a monograph on the technique of eight or nine operations. Nothing more is pretended. Nothing is said about indications, after-care or results. The book is very readable and the illustrations so clear that one feels after reading it that one has had the pleasure of watching at close quarters a day's operating by a master.

A. S. Duncan

REVIEW OF CURRENT LITERATURE

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ANATOMY AND PHYSIOLOGY

261. **Studies of the Human Trophoblast in Tissue Culture. I. Cultural Methods and Histochemical Staining.** By H. A. THIEDE. *Amer. J. Obstet. Gynec.*, **79**, 636–647. Apr. 1960. 11 figs. 21 refs.

The author describes a method of growing human trophoblast in monolayer on glass without placental explants and the subsequent histochemical staining of the cells. Previous investigations have left it doubtful whether the cells in placental explants that secrete chorionic gonadotrophin are Langhans cells. Chorionic villi were obtained by dissecting them off the chorionic plates from cases of therapeutic abortion between 9 and 14 weeks, each placenta yielding 25 to 30 cultures; within 24 hours a large population of cells which almost certainly come from the chorionic villi was growing on the cover slip and amongst them three cell types could be distinguished. Bio-assays of the nutrient media revealed chorionic gonadotrophin in amounts sometimes exceeding 20,000 I.U. per litre but its exact origin is still undetermined.

The article includes beautiful illustrations of the different cell types, and tissue culture and staining techniques are described in detail. *F. J. Browne*

262. **Clinical Aspects of Progesterone Metabolism.** By A. KLOPPER. *Ann. Ostet. Ginec.*, **82**, 421. Apr. 1960. 15 figs.

A new and much more accurate method of estimation of urinary pregnanediol has been devised and this has been used to study the metabolism of progesterone.

A surprising finding was the presence of appreciable amounts of pregnanediol in male urine. It was decided that this was a by-product of corticosterone metabolism and this was proved by showing that after a two-stage adrenalectomy pregnanediol was no longer found in the urine. Also in the absence of the adrenals, administration of A.C.T.H. no longer stimulated increase of pregnanediol excretion.

Studies of the conversion of progesterone to pregnanediol showed that when progesterone is injected 11 to 14 per cent of it excreted as progesterone. No evidence could be found of the "progesterone priming" described by some authors. In a few cases however the conversion rate falls well below the usual 11 to 14 per cent. Reduction of progesterone to pregnanediol and subsequent conjugation of the latter with glycuronic acid is believed to take place in the liver. Study of patients with severe liver damage such as acute hepatitis or metastatic carcinoma showed normal pregnanediol excretions.

Pregnanediol has been recovered from the faeces of a pregnant woman in the unconjugated form. In the bile recovered from biliary drainage after cholecystectomy pregnanediol was recovered in the conjugated form. However, it has been proved that negligible amounts of pregnanediol are in fact re-absorbed from the gut.

The level of pregnanediol excretion in any patient is the result of several processes of which progesterone production is only one. Any single determination must therefore be regarded with reserve and considerable day to day variations in pregnanediol output may occur in normal physiological circumstances. *Josephine Barnes*

263. **Electrolyte in Human Myometrium.**

By E. E. DANIEL, J. HUNT, D. ALLAN and K. ROBINSON. *Amer. J. Obstet. Gynec.*, **79**, 417–427. Mar. 1960. 4 tables. 26 refs.

Electrolyte concentration in the non-pregnant human myometrium is of interest because of differing opinions regarding its activity in the secretory phase of the cycle, while that in pregnancy is of interest because of the claim that pregnancy is associated with loss of myometrial potassium and gain of sodium and that the loss of potassium and gain of sodium are accentuated in prolonged labour. These findings however have not been confirmed and the only change found in labour is in water concentration. Differences in electrolyte concentration might underlie the variation in activity of different parts of the uterus.

In the present study post-menopausal uteri, which might be regarded as uninfluenced by ovarian activity were found to have a high concentration of sodium and chloride and low concentrations of potassium and water at all parts of the uterus. In the late proliferative phase of the menstrual cycle the myometrium contained less sodium and chloride but more potassium and water, and the elevation of potassium was relatively greater in the upper and middle segments than in the lower segment. In the secretory phase the concentration of potassium tended to be still higher. These results provide no support for the hypothesis that progesterone diminishes the potassium content of uterine muscle cells or antagonizes the action of oestrogens on uterine contractility in the human.

In the myometrium during normal labour potassium concentration is still high, but in two cases of prolonged labour both potassium and water concentrations were very low. In a third case, however, concentration of potassium was high, which suggests that when potassium is low it is the effect of prolonged labour rather than the cause. In myometrium obtained at elective Caesarean section at term the concentration of electrolytes and water closely resembled that in the late secretory endometrium; potassium concentration was slightly less in the mid-segment than in the upper, and considerably less in the lower segment than in the middle. These data suggest the existence of a chemical gradient from fundus to cervix which might influence uterine activity.

F. J. Browne

PREGNANCY

264. **The Influence of Occasional Factors (Meteorological Changes, Age and Parity) on Toxaemia of Pregnancy.** (Influenza di fattori occasionali (Alterazione meteorologiche, eta e parita) sulle tossicosi gravidiche.)

By C. FERRARO, L. STURA and L. STRINGA. *Ann. Ostet. Ginec.*, **82**, 263. Mar. 1960. 22 refs.

A ten-year study, from 1949 to 1958, has been made on the incidence and occurrence of toxaemia of pregnancy, correlated with meteorological changes, age and parity.

It is found that sudden changes in barometric pressure, whether rise or fall, tend to be associated with an increased incidence of toxaemia. Increase of atmospheric humidity is also related to these changes. No other climatic changes appeared to be important. The authors realize that these changes are not in any way causative but they believe they may aggravate a pre-existing tendency to toxaemia.

Toxaemia is found to have a greater incidence in older mothers, the curve rising sharply after the age of forty. On the other hand the incidence of toxaemia falls with each succeeding pregnancy and is negligible in women in their eighth pregnancy. *Josephine Barnes*

265. **The Haemorrhagic Syndrome in Obstetrics due to Afibrinogenaemia.** (Hemorragica in ostetricia da afibrinogenemia.)

By F. RAITI. *Ann. Ostet. Ginec.*, **82**, 299. Mar. 1960. 21 refs.

Two cases of afibrinogenaemia are described, both occurring after the expulsion of a dead foetus. In both cases, emergency hysterectomy was performed for uncontrollable bleeding and one patient died. Fibrinogen does not appear to have been given perhaps because it was not available.

The aetiology, diagnosis and treatment of the condition are discussed and it is concluded that hysterectomy should only be performed as a desperate measure when other methods of treatment fail. *Josephine Barnes*

266. **Erythrocyte Production and Destruction During Pregnancy.**

By J. A. PRITCHARD and R. H. ADAMS. *Amer. J. Obstet. Gynec.*, **79**, 750–754. Apr. 1960. 3 tables. 3 figs. 16 refs.

The authors failed to confirm previous reports that in normal pregnancy there is some depression of bone marrow and conclude that at least in the latter half of pregnancy red cell and haemoglobin production are increased while the life span of red cells is unchanged. At term, or shortly before, the total red cell volume exceeds that of comparable non-pregnant women by 25 per cent, and this is accompanied by a progressive shift towards younger red cell age. In all pregnant subjects, both anaemic and non-anaemic, the rate of incorporation of iron into red cells was much greater than in the non-pregnant. Occasional patients with iron

deficiency anaemia do not respond to iron therapy but the authors suggest that, as in some of their cases, this may be due to a chronic infective condition or chronic renal disease rather than, as R. G. Holly has claimed, to a factor or factors associated with pregnancy which can cause a temporary marrow depression and interference with its ability to manufacture red cells and haemoglobin.

F. J. Browne

267. **The Use of Relaxin in the Management of the Retained Dead Fetus.**

By J. G. MACLURE and J. H. FERGUSON. *Amer. J. Obstet. Gynec.*, **79**, 801–804. Apr. 1960. 2 tables. 18 refs.

This is a study of 20 patients with missed abortion in whom the length of foetal death varied from 3 to 140 days, the average being 40 days. Relaxin in the form of Releasin (Warner Chilcott Laboratories) was given intramuscularly in 5 doses of 60 mg. each every 2 hours, followed by a sixth and final injection of 20 mg. In 16 of the 20 cases the cervix was judged to have become softened and in all these a pitocin drip was successful in causing evacuation of the uterus within a few hours. There was no post-partum or other haemorrhage in any of the cases. The authors consider the method worth further trial.

F. J. Browne

268. **Unequivocal Radiological Evidence of Intra-uterine Foetal Death Including Demonstration of Gas Formation Within the Foetal Circulation. Report of Case and Review of 37 Cases of Foetal Death.**

By R. BENNETT. *Clin. Radiol.*, **11**, 200–204. July 1960. 1 table. 6 figs. 28 refs.

Recognized radiological signs of intra-uterine death are reviewed and the author seeks to discover the most constant sign of irrefutable intra-uterine death, paying special attention to the frequency of finding gas in the foetal circulation.

Special references are made to:

Spalding's sign (1922): over-riding of skull bones with asymmetry.

Hartley's sign (1939): foetus rolled up in a ball.

Thom's sign (1940): angular kyphosis of the spine.

Roberts' sign (1944): gas in foetal circulatory system.

Deuel's sign (1947): "halo sign" showing increase in width of scalp tissues.

Borell and Aernström's sign (1958): disalignment of skull bones at coronal and lambdoidal sutures before the tenth month of pregnancy and prior to the onset of labour.

A case report is given and a review is made of the pre-partum X-rays of 37 cases of foetal death to discover the most consistent and reliable signs. These proved to be:

(1) Disalignment or overlap of cranial bones.

(2) Lack of foetal tone.

These two signs were present in over 80 per cent of cases. Gas was present in 5 cases (14 per cent) and the "halo sign" in 7 (20 per cent). No radiological sign of intra-uterine death was found in 5 (14 per cent). In no case was gas found without other good evidence of intra-uterine death. An analysis of the characteristic appearance of gas formation in the vessels is given as well as pitfalls in diagnosis. The radiological technique for demonstrating gas is briefly described. Mention is made of the fact that some 70 cases of gas in the foetal circulation in intra-uterine death have now been reported.

Robert Percival

269. **Vascular Collapse Complicating Septic Abortions.**

By L. L. ADCOCK and E. Y. HAKANSON. *Amer. J. Obstet. Gynec.*, **79**, 516–525. Mar. 1960. 6 figs. 114 refs.

The authors describe 6 cases of this condition in which the appearance of vascular collapse and shock without significant blood loss establishes the diagnosis. The shock is preceded by rigors and a spiky and often very high temperature. All the clinical features of shock are present including hypotension, pallor, rapid thready pulse, sweating and often a falling temperature. Blood cultures may or may not be sterile. Pulmonary oedema, toxic hepatitis with jaundice, uraemia, suppurative pelvic peritonitis and bacterial endocarditis and myocarditis are frequent sequelae.

Most authorities advocate conservative therapy in septic abortion unless there is severe bleeding on the basis that infection is still further spread by interference which breaks down the natural barriers to infection in the uterus and parametrium, and there is no doubt that this occurs with curettage. Nevertheless the authors favour active interference with removal of infected tissue and drainage within 12 hours after admission. If vascular collapse is already present the blood pressure should be supported at a level sufficient for urinary secretion by intravenous infusion of a vasopressor agent such as norepinephrine or metaraminol through a polyethylene catheter. Blood and uterine cultures with sensitivity tests should be obtained on admission and before starting antibiotics. The organisms responsible are most often *E. coli.*, proteus vulgaris, coli aerogenes and sometimes strepto- and staphylococci. Pitocin may be effective in completing the abortion and usually controls bleeding. Other measures such as oxygen, correction of electrolyte disturbances, blood transfusion and administration of digitalis in cardiac decompensation are essential. Of the 6 cases recorded 2 died, one after active and the other after conservative management of the septic abortion.

F. J. Browne

270. **Herpes Gestationis. A Report of 2 Cases.**

By S. P. WEGRYN, R. A. MARKS and J. R. BAUGH. *Amer. J. Obstet. Gynec.*, **79**, 812–814. Apr. 1960. 5 refs.

Both these cases were cured by intramuscular injections of reticulose (Lipoprotein—nucleic acid) which is a protein complex combining a protein with organic lipids and nucleic acid. Its mode of action is to enhance and accelerate leucocytic response, increase antibody production and stimulate phagocytosis. The recommended dose is 2 ml. intramuscularly every 4 to 6 hours

but doses should be adjusted to clinical findings. In both cases there was marked symptomatic relief in a few days and the lesions cleared up in about 2 weeks.

F. J. Browne

271. **Ectopic Ureter Syndrome Commencing in Pregnancy.**

By J. H. LEVACK. *Brit. J. Urol.*, **32**, 152–155. June 1960. 3 figs. 6 refs.

A patient aged 37 years had incontinence of urine with occasional haematuria ever since the birth of her only child 14 years previously. There also had been attacks of "pyelitis" with left loin pain.

Before the pregnancy there were a few bouts of bed wetting which were regarded as of no consequence. Intravenous pyelography revealed a double kidney on the left side and two ureters but at cystoscopy only one ureteric orifice was discovered. Eventually the opening of an ectopic ureter was found just distal to the vesical orifice on the left side. This was catheterized and the atrophic half of the double kidney discovered. The patient was operated on and a segment of the ureter of the atrophic kidney removed. Partial nephrectomy was not done because of a bizarre distribution of the blood supply.

Several cases had been reported in the literature where incontinence due to ectopic ureter had been started as a result of pregnancy. Probably the changes associated with pregnancy are responsible for this.

The literature on the subject is being reviewed.

J. H. Carver

272. **Anastomoses of Chorionic Villi as a Result of Placentitis.**

By Y. ISHIZAKI. *Obstet. and Gynec.*, **15**, 602–611. May 1960. 13 figs. 35 refs.

In the latter half of gestation there are adhesions between chorionic villi which become more numerous as pregnancy advances. Less often, villi are glued together in intervillous thromboses and in foci of placentitis. Intervillous thrombi become surrounded in time by syncytiotrophoblasts whilst cytotrophoblasts invade the masses of debris of red blood cells; eventually the entire lesions are converted into intervillous trophoblastic islands, some of which undergo liquefactive degeneration. The same thing appears to happen to intervillous fibrin deposits.

In sharp contradistinction, in the focus of placentitis, marked proliferation of fibroblasts and angioblasts is recognizable, until ultimately injured villi are reconstructed into a large new villus in which fibrovascular stroma connects one villus with another. When involved villi happen to contain calcified syncytial knots, the latter may survive the destruction by inflammation and remain ("orphan bodies") as marks of healed placentitis.

Most foci of placentitis appear to be small, scattered lesions on non-specific inflammation, probably caused by haematogenous dissemination following trivial infections such as common cold, sore throat and tonsillitis.

J. G. Dumoulin

273. **Isolated Vestiges of Calcified Syncytial Knots ("Orphan Bodies") in the Stroma of Chorionic Villi.**

By Y. ISHIZAKI. *Obstet. and Gynec.*, **15**, 528–534. Apr. 1960. 15 figs. 7 refs.

During routine examinations of placentae, calcified vestiges of syncytial knots were found by the author in the stroma of chorionic villi. Upon examination of serial sections these were found to have no connexion with the trophoblastic layers covering the villi. Studies suggest that these structures had been calcified syncytial knots of chorionic villi which were later involved in placentitis. When the villi were destroyed by the inflammation the calcified syncytial knots were left alone within a conglomerate mass of exudates and injured villi. With the healing of placentitis the focus is organized into a new villus, in which the calcified knots became sequestered. The vestiges are thus telltale marks of sites of healed placentitis. This fact introduced the possibility of the formation of fibrovascular anastomoses among the villi glued together in the focus. The term "orphan bodies" has been given to these vestiges which were found in 43 per cent of 270 placentae examined.

J. G. Dumoulin

274. **Contribution to Cytological Diagnosis of the Expected Date of Delivery and of Prolonged Pregnancy.** (Beitrag zur Zytodiagnostik des Geburtstermins und der verlängerten Schwangerschaft.)

By J. ZIDOVSKY. *Zbl. Gynäk.*, **82**, 513–523. Apr. 2, 1960. 1 table. 10 figs. 17 refs.

The author reports on cytological studies of vaginal smears in 48 pregnant women. Twenty-three cases were dismissed because of various forms of vaginal pathology (vaginal infections, cervicitis), leaving 25 "healthy" patients whose vaginal smears were studied weekly from the 34th week until delivery. It was found that in normal cases before the 39th week the cells were mostly basophile with a predominance of navicular and intermediate cells. Leucocytes were scanty. Shortly before delivery (in some cases occurring in the 42nd week) a considerable change occurs: navicular cells become scarce, the proportion of intermediate and superficial cells with vesicular and pyknotic nuclei rises, as does the incidence of leucocytes. On these findings the author classifies four types of normal vaginal smears in pregnancy, from which it can be decided whether a given case is biologically (not necessarily chronologically) (1) in late pregnancy; (2) shortly before term; (3) at term; (4) verging on labour. In Class 4 cases navicular cells are absent, the incidence of superficial cells is 40–80 per cent, the number of leucocytes is increased, the incidence of eosinophilia reaches 20 per cent, the pyknotic index varies between 20 and 40 per cent.

Using this classification a further 427 women were studied in 2,834 vaginal smears. In patients whose smears were graded as Class 1 labour was unlikely to begin in less than 10 days. With Class 2 smears, labour was expected within 4–8 days; with Class 3 smears it was likely within 1–5 days; with Class 4 smears it started on the same day, or at the latest, within 3 days. On this basis the forecast of the date of birth was correct in 88 per cent of patients.

In 173 prolonged pregnancies assessment by the vaginal smear method and by digital examination of the cervix was followed in 98·8 per cent by a successful induction of labour.

In view of the claims of Ezes (*Ann. Endocr.* (*Paris*), 1957, **14,** 463), it is of interest to note that the author found no correlation between the incidence of parabasal cells in 76 cases of prolonged pregnancy and hazards to the child due to postmaturity. Not one of the children suffered any major or minor deleterious effect. The author did, however, find that when in 11 other cases the child was born dead or in a hypoxic condition the cytological picture had remained in Classes 3 or 4 for a longer time than was expected by comparison with the normal series, i.e., more than 5–6 days. In fact, usually it amounted to 8 to 14 or even 16 days.

The author concludes that the foetus is in danger of hypoxia whenever Class 3 or 4 smears persist for more than 3 to 6 days.

Bruce Eton

LABOUR

275. **The Clinical Value of External Tocography in Practical Obstetrics.** (Über die Bedeutung der äusseren Wehenmessung im Rahmen der klinischen Geburtshilfe.)

By H. Siener. *Zbl. Gynäk.*, **82,** 580–585. Apr. 16, 1960. 2 figs. 12 refs.

The author recorded simultaneously the progress in cervical dilatation, descent of the presenting part and external tocography during labour. External tocography provides perhaps more a qualitative than a quantitative assessment of uterine activity because it is not certain whether it registers changes in (*a*) the tension of the uterine wall; (*b*) the intra-uterine tension; or (*c*) forward bulging of the uterus. Nevertheless, the author found that there was a parallel behaviour between tocographic records and dilatation of the cervix, provided that distinction was made between an initially soft or rigid cervix.

External tocography has at least three clinical values: (1) it enables the obstetrician at any time to form a clear impression of the quality of uterine contractions by inspection of the graph. This gives a more objective picture than a clinical assessment which often is a matter of individual opinion; (2) tocographic records are particularly instructive for the evaluation of the effects of oxytocic, spasmolytic and analgesic drugs; (3) for the safe use of continuous intravenous infusions of oxytocic drugs tocographic control is almost indispensable.

Bruce Eton

276. **Effect of the Relaxing Hormone on the Labouring Human Uterus.**

By W. G. Slate and W. F. Mengert. *Obstet. and Gynec.*, **15,** 409–414. Apr. 1960. 5 tables. 2 figs. 2 refs.

Two thousand patients were followed through labour, half of them being given intramuscular injections of Relaxin, the other half being used as controls.

The two groups appeared to be similar in all respects. The conclusion reached was that Relaxin had no significant effect on labour. In fact, the results of this well-controlled experiment suggest that Relaxin administered in labour does not affect the contractions of the human uterus.

J. G. Dumoulin

277. **The Prophylactic Administration of Ergometrine and Hyalase and the End of the Second Stage of Labour.** (Die profilaktiese toediening van ergometrien met hialase aan die einde van die tweede stadium van kraam.)

By J. N. de Villiers and J. P. du Toit. *S. Afr. med. J.*, **34,** 561–563. July 2, 1960. 6 tables. 3 figs. 7 refs.

By comparing the results of 3 groups of cases we found that prophylactic ergometrine and hyalase given intramuscularly before the birth of the baby, and preferably with the crowning of the head, reduces the duration of the third stage as well as the amount of haemorrhage, thereby reducing the incidence of post-partum haemorrhage from 11·98 per cent (where no ergometrine is given before delivery of the placenta) to 4·8 per cent.

There is at the same time an increased incidence of retained placenta from 0·87 per cent to 1·7 per cent and an increased rate of manual removal of the placenta from 0·65 per cent to 1·35 per cent. This increase is so slight that in our opinion it is outweighed by the advantage of a significantly lessened incidence of post-partum haemorrhage.

Abruptio placentae, fibroids, prolonged labour and twin pregnancy were found to predispose to post-partum haemorrhage. In these cases it is therefore advisable to give prophylactic ergometrine intravenously with the crowning of the head. In twins this should obviously only be given with the birth of the second baby.

Authors' Summary

278. **Epidural Anaesthesia in Obstetrics.**

By C. R. Climie. *N.Z. med. J.*, **59,** 127–130. Mar. 1960. 6 refs.

In the period of one year, November, 1958–October, 1959, at the National Women's Hospital there were 2,564 deliveries, among which were 331 forceps deliveries. General anaesthesia was used for only 28 of these cases. The great majority (257) were delivered with a pudendal nerve block. For 66 forceps deliveries a lumbar epidural block was used. The author proceeds to describe the technique used for epidural block, and gives the results in 93 patients who received this treatment.

The reasons were as follows: forceps deliveries—66; Kielland's rotation of P.O.P.—32; manual rotation of P.O.P. followed by forceps delivery—16; forceps delivery —13; assisted breech delivery with forceps to the after-coming head—2; examination under anaesthesia—3. Continuous epidural block over several hours in prolonged labour—11 cases; four of these eventually had Caesarean section. Epidural block was used for Caesarean section in 20 cases.

Complications were as follows:

Failure to establish analgesia—one due to puncture of the dura, one due to superficial injection.

Hypotension—in three cases, all forceps, methylamphetamine was administered to raise the blood pressure.

Infection—there was evidence of infection around the site of needle puncture in one case. Erythromycin was administered.

Neurological sequelae—one case of post-partum foot drop occurred following a mid-forceps delivery. It was considered that epidural anaesthesia was not to blame for this accident. *L. Woodrow Cox*

LACTATION

279. **Current Trends in Breast Feeding.**

By M. McGEORGE. *N.Z. med. J.*, **59**, 31–41. Jan. 1960. 1 table. 2 figs. 95 refs.

The author discusses breast feeding practices in different countries throughout the world. He then gives, in detail, the incidence of breast feeding from 24 maternity units in New Zealand. The proportion of mothers fully breast feeding on discharge from the maternity unit varied from 92 per cent to 62 per cent, but in the majority of cases was between 70 per cent and 80 per cent. The relatively wider variation noted in the incidence of artificial feeding appeared to reflect the varying importance attached to complementary feeding in individual hospitals. During the past 12 years the proportion of mothers fully breast feeding on discharge from the Queen Mary Maternity Hospital, Dunedin, decreased from 89 per cent to 75 per cent. The mothers were examined again at the Post-Natal Clinic six weeks after delivery and it was found that, over the same 12 years, the proportion of infants that had been weaned increased from 15 per cent to 40 per cent. It is evident that an increasing proportion of mothers wean their infants shortly after they return home.

The author then discusses the importance of breast feeding and the reasons for failure to maintain breast feeding. He concludes that artificial feeding conducted according to modern standards appears to have become as safe as breast feeding, so far as freedom from infection is concerned. He suggests that human milk has certain advantages over modified cow's milk for premature and for delicate infants. He considers that when breast feeding becomes inadequate or difficult there should be no hesitation in changing to artificial feeding. Both infant and mother can suffer unnecessarily as the result of unwisely prolonging inadequate breast feeding. The suggestion that results will only improve if the individual mother is encouraged and assisted is made. It seems important to take an interest in the mother at the beginning of pregnancy and to encourage her personally throughout the pregnancy, and, once again, to supervise lactation at its establishment. *L. Woodrow Cox*

INFANT

280. **The Relationship Between Chemical Changes in the Blood and the Onset of Respiration in the Newborn.** (Die Bedeutung chemorezeptiver Impulse für den Atembeginn bei Neugeborenen.)

By H. WULF. *Geburtsh. u. Frauenheilk.*, **20**, 473–478. May 1960. 2 tables. 25 refs.

The oxygen and carbon dioxide tensions and the pH of blood in the umbilical vein were measured in 36 infants immediately after their delivery and at the onset of respiration. It was found that the average fall in oxygen tension was 11·5 mm. Hg; that the average rise in carbon dioxide tension was 1·5 mm. Hg; and that the average fall in pH was 0·015. The author believes that these chemical changes are important factors in the initiation of respiration in the newborn.

[The details of the experimental technique have been reported elsewhere (*Klin. Wschr.*, 1958, **36**, 234; *Z. Geburtsh. Gynäk.*, 1959, **152**, 98). The author does not state the time lag between birth and the onset of respiration, but he makes the statement that the average latent period is usually 30 seconds and not longer than 1½ minutes in normal infants.] *Peter J. Huntingford*

281. **The Value of Various Methods of Artificial Respiration in the Treatment of Asphyxia of the Newborn.** (Der Wert verschiedener Beatmungsmethoden bei der Behandlung der Neugeborenenasphyxie.)

By C. F. MICHEL. *Zbl. Gynäk.*, **82**, 625–629. Apr. 23, 1960. 21 refs.

The physiological principles underlying various known methods of artificial respiration are discussed. After insertion of an endotracheal tube in asphyxiated neonates, the author was unable to demonstrate any movement of air at the open end of the tube by methods of respiration based on compression of the thorax, or by methods which raise and then lower the abdominal organs.

In the discussion of positive pressure methods the author favours those involving the use of an endotracheal tube. Since he adopted the practice of raising the pressure slowly rather than jerkily he has not met any more cases of rupture of pulmonary alveoli.

The objections to mouth-to-mouth breathing are investigated. It is wrong to think that this method provides the child with air rich in carbon dioxide and poor in oxygen, because the initial air which enters the child's respiratory tract comes from the dead space of the attendant's air passages. *Bruce Eton*

282. **The Control of Body Temperature in Newborn and Premature Infants After Spontaneous and Operative Delivery.** (Die Temperaturregelung Neugeborener und Frühgeborener nach spontaner und pathologischer Geburt.)

By K. BRÜCK, M. BRÜCK and H. LEMTIS. *Geburtsh. u. Frauenheilk.*, **20**, 461–472. May 1960. 1 table. 5 figs. 18 refs.

The authors, working in the University Gynaecological Clinic, Marburg, have studied the variations of body

temperature, cutaneous blood-flow and oxygen consumption of newborn infants. For this purpose they used a specially heated chamber; the temperature of the baby and of the chamber and cutaneous blood flow were recorded continuously by means of thermo-couples; the oxygen and carbon dioxide content of the air leaving the chamber were analyzed. It was found even with immature infants that cooling down to 23° C. evoked an increase in the output of body-heat sufficient to maintain the body temperature at 37° C. This ability to increase heat production in order to maintain body temperature was relatively greater than in adults. The immature infants were however unable to reduce cutaneous blood-flow effectively and this therefore led to greater heat loss and eventually to a fall of body temperature. The authors consider that the optimum environmental temperature for immature infants lies between 30°–32° C. After difficult forceps deliveries or Caesarean section it was found that the infants' ability to increase heat production in response to cooling was definitely impaired.

Peter J. Huntingford

283. **Studies in the Transmission of Maternal Isoantibodies in Children Delivered by Caesarean Section.** (Untersuchungen über den Übertritt der mütterlichen Isoantikörper bei Kaiserschnitt-Kinder.)

By W. Mosler. *Zbl. Gynäk.*, **82**, 485–489. Mar. 26, 1960. 3 refs.

The blood groups of mother and child were determined in 334 cases and the difference between the maternal and foetal blood titres of haemolysins in saline and in colloidal ("Periston") solution was estimated in the various combinations of groups between mother and child. The difference in titres between saline and Periston in the various combinations averaged two levels in the foetal serum, whereas it differed by only one level in the maternal serum. This difference between the maternal and foetal serum suggests that the incomplete antibody detected in colloidal solution passes through the placental barrier more readily than the antibody demonstrated in saline.

As Sander (*Z. Geburtsh. Gynäk.*, 1955, **143**, 1) maintained that the antibodies found in cord blood enter the foetal circulation as a result of placental separation, the author obtained blood in 11 cases from the child's end of the cut umbilical vein immediately after delivery by Caesarean section, before separation of the placenta.

It was found that maternal isoantibodies were already present in the child's blood at the time of Caesarean sections. The Periston-titre of antibodies was comparatively higher than the saline titre. The author attributes this observation to the larger size of the molecule of saline antibodies, being prevented more effectively from passing through the placental barrier.

Bruce Eton

284. **Diagnosis of Gonadal Dysgenesis in Newborn Infants.**

By R. M. Richart and K. Benirschke. *Obstet. and Gynec.*, **15**, 621–624. May 1960. 6 figs. 11 refs.

Four cases of gonadal dysgenesis (Turner's syndrome) in the newborn period are presented by the authors. The diagnostic features are oedema of the hands and feet, webbing of the neck, short neck, whorled hair at the base of the skull, and hair growing far down the neck.

J. G. Dumoulin

285. **Is Prolonged Treatment with Cortisone in Pregnancy Dangerous for the Child?** (Ist eine langdauernde Cortisonbehandlung in der Schwangerschaft für das Kind gefährlich?)

By O. Preisler. *Zbl. Gynäk.*, **82**, 657–659. Apr. 30, 1960. 28 refs.

Experimental evidence in animals has shown that cortisone administered during pregnancy, may be followed by foetal malformations, intra-uterine death or abortion. It would therefore be of interest to find out whether similar risks are incurred when using cortisone in human pregnancy.

The author reports on two children whose mothers were treated with cortisone on account of Rhesus antibodies which had caused several previous stillbirths. The patients were given 1,000 mg. of "Depot-Cortison" every 10 days from the 15th week of pregnancy onwards and 20–40 units of "Depot-A.C.T.H." every 10 days until term. Each patient therefore received a total of 18 g. of cortisone and 540 units of A.C.T.H. The children were born spontaneously, they were healthy and have, so far, developed normally in accordance with their age ($2\frac{1}{2}$ and $3\frac{1}{2}$ years). Both had replacement transfusions after delivery. No malformation was observed in either child.

In a third case similarly treated the child died 2 hours after delivery at the end of an exchange transfusion. Post-mortem examination showed massive inhalation of liquor and anoxic changes. Histological examination of the suprarenal glands did not show any atrophy such as is observed in the adult after administration of cortisone.

[Although the report of the absence of any harmful effects in only three cases is of interest, it would have been more valuable if the genotype of the fathers had been given and if details had been supplied of the extent to which the previous children were affected, so that the reader could form an impression of the chances of survival of the three children had cortisone not been given.]

Bruce Eton

286. **Diabetic Embryopathy.**

By W. P. U. Jackson. *S. Afr. med. J.*, **34**, 151–152. Feb. 20, 1960. 13 refs.

The author describes the clinical features of the baby produced by the diabetic mother. These babies are overweight, over-long and over-fat; they are oedematous and lose a lot of fluid in the first week; there is cardio- and hepato-megaly, an expanded erythron with widespread haematopoeisis and a high haemoglobin content. The general appearance is that of Cushing's syndrome. They are feeble and behave as premature infants, susceptible to birth trauma, infection and hyaline membrane disease.

Intra-uterine death is common, and these stillbirths are distinguished by active hepatic haematopoeisis as in erythroblastotic infants. Luteal cysts may be found in the ovaries. Almost invariably the islets of Langerhans are large with an increase in the beta cells. It seems as if the pancreas of the diabetic's infant may contain up to 30 times the normal amount of insulin. In Boston and Brussels the foetal loss in the mild diabetic is apparently very much less. In Cape Town the tendency to produce stillbirths and large babies extends back indefinitely into the past obstetric life of the diabetic woman, in her pre-diabetic phase. The mean percentage of islet tissue is normally 1·3 per cent. This rises to about 7 per cent in erythroblastotics and in children of diabetic and pre-diabetic mothers. There is no tendency for women in the early stages of acromegaly or Cushing's syndrome to produce large babies or stillbirths, and this is surely strong evidence against either a growth hormone or glucocorticoids being the sole cause of the embryopathy. A number of babies may be saved if the diagnosis of prediabetes is suspected and the suspicion acted upon.

L. J. Abramowitz

287. **Is Acute Angulation of the Foetal Spine Necessarily a Sign of Intra-uterine Death or Congenital Malformation?** (Beweist eine röntgenologisch festgestellte starke Abknickung der kindlichen Wirbelsäule in utero einen intrauterinen Fruchttod bzw. eine Missbildung?)

By W. KUPFERSCHMID and H. HORNIG. *Geburtsh. u. Frauenheilk.*, **20,** 456–460. May 1960. 3 figs. 23 refs.

A case is reported in which acute angulation of the foetal vertebral column was seen on an X-ray before the onset of labour; the patient was delivered of a healthy infant; and investigations after birth revealed no abnormality. The author points out that care must be taken in the interpretation of this radiographic appearance as a sign of intra-uterine death or of gross congenital malformation, e.g., spina bifida.

Peter J. Huntingford

288. **The Problem of Postmaturity.** (Contributo clinico-statistico alla gravidanza protratta. Nuove possibilita di diagnosi.)

By P. MENTASTI. *Minerva ginec.* (*Torino*), **12,** 196–210. Feb. 29, 1960. 13 tables. 175 refs.

There is still much confusion and difference of opinion on this subject and on its management, and statistics given by various authorities show marked divergencies. There are schools of interventionists and of a policy of *laissez faire*, and all are prepared to produce convincing statistics and arguments. [The number of "references" at the end of the paper bears witness to this.] The condition and apparent maturity of the baby at birth does not always accord with that expected from the Naegele calculation. This state of affairs may be related to the mother's menstrual type, whether her intervals are shorter or longer than normal, whether her menarche was early or late. It is conceivable that some women also need a shorter or longer time to mature their babies than others. Babies can be clearly postmature to the eye, and suffer the very serious risks entailed, whilst others carried *in utero* well beyond D-day are perfectly healthy or even premature in appearance. All this has resulted in babies being classed as immature, premature, normal megalosomic and microsomic, hyper- or super-mature, postmature (eutrophic or dystrophic), etc. Reliance, in the author's opinion, cannot be placed on the following—diminished maternal abdominal circumference, fall in maternal weight, decrease in pregnanediol excretion, modification of vaginal cytology, or even in the character of the liquor amnii obtained by amniocentesis. The author has for three years used electrophoretic analysis of the mother's serum proteins and related this to the physical evidence of the baby's maturity and of the calendar calculation. He has found this a reliable indication. Beyond term there is a progressive increase in alpha-2 globulin (the first sign) followed by increase in gamma-globulin. He regards these signs as evidence of developing placental insufficiency and degeneration, showing that the well-being of the baby is being compromised and affording an indication for intervention in its interests.

W. C. Spackman

289. **Foetal Haemoglobin Concentration in the Cord Blood of Children Born after Prolonged Pregnancy.** (Der fetale Hb-Gehalt im Nabelschnurblut bei Neugeborenen mit verlängerter Tragzeit.)

By E. NEUMAYER. *Zbl. Gynäk.*, **82,** 481–485. Mar. 26, 1960. 2 tables. 1 fig. 14 refs.

The author determined the percentage of foetal haemoglobin in the cord blood of 50 children born at term and of 31 delivered after a prolonged pregnancy (292 or more days after the onset of the last menstrual period). The blood was obtained by puncture of the umbilical vein, immediately after the birth of the child. The tests were performed according to the method of Brinkham and Jonix (*J. Physiol.* (*Lond.*), 1935, **85,** 117), modified by Singer, Chernoff and Singer (*Blood*, 1951, **6,** 413). Foetal haemoglobin determinations were carried out in triplicate with the spectrophotometer.

The mean percentage of foetal haemoglobin amongst the 50 children born at term was 77·9 per cent, with a range of 65·3 to 89·4 per cent. Amongst the 31 cases of prolonged pregnancy, the mean value was 69·4 per cent, with a range of 52·2 to 87·0 per cent. The difference is statistically significant.

Bruce Eton

OBSTETRIC OPERATIONS

290. **Experiences with the Vacuum Extractor of Malmström.** (Anwendung und Erfahrungen mit dem Vakuum-Extraktor nach Malmström.)

By H. KRABISCH. *Zbl. Gynäk.*, **82,** 673–677. Apr. 30, 1960. 2 tables. 21 refs.

The author has been using the vacuum extractor since October, 1957 and reports on 56 women delivered with this instrument, an incidence of 0·68 per cent amongst 8,207 children born.

The main indications for using the extractor were secondary inertia with failure of progress and maternal exhaustion, particularly in elderly primigravidae with rigid soft parts, pre-eclamptic toxaemia, eclampsia, high head with incomplete dilatation of the cervix and threatened intra-uterine asphyxia.

The advantages claimed for the instrument compared with the forceps are the avoidance of pressure by the blades of forceps on the foetal head and of trauma to the maternal tissues, and simplicity of application without the need for general anaesthesia. The instrument can also be used when forceps delivery is not possible in cases of an incompletely dilated cervix. It was used in 18 such patients.

A disadvantage of the vacuum extractor is without doubt the trauma to the foetal scalp. Apart from minor signs of pressure which disappeared within 1–2 days, some cases of slight ulceration were observed and in one child necrosis of the traumatized area of the scalp occurred which was attributed to the labour having lasted an unduly long time.

Two children died; one death was attributed to eclampsia and diabetes and the other to disproportion, the child weighing 11 pounds. The author claims that these deaths were not due to the vacuum-extractor but he makes no mention of any post-mortem examination.

Follow-up examination was carried out in 26 children; four of these showed a scar on the occiput and one had an area of alopecia.

Bruce Eton

291. **Sequelae of Caesarean Section.**

By H. P. DUNN. *N.Z. med. J.*, **59**, 180–183. Apr. 1960. 8 tables. 11 refs.

The study was based on clinic patients having Caesarean sections in the years 1955 and 1956. Among 4,194 deliveries, the incidence of Caesarean section was 6·6 per cent.

Two hundred and fifty-five Caesarean sections were analyzed. Of these, 79 were emergency admissions. The indications for operation were: repeat section, 94; placenta praevia, 46; disproportion, 38; previous vaginal repair operations, 13; pre-eclampsia and hypertension, 9; transverse lie, 9; uterine inertia, 8; breech presentation, 7; foetal distress, 7; brow presentation, 5; elderly primigravida, 4; various uncommon indications, 13. The lower segment operation was performed 249 times, the classical 3 times and Caesarean hysterectomy 3 times. The perinatal mortality was 16 in the 255 cases.

A questionnaire was sent to the patients asking for information about subsequent pregnancies, miscarriages, sterility, operations, menstruation and psychological disturbances. They were also invited to make comments, criticisms or suggestions about their hospital experiences. One hundred and seventy-three replies were received with varying degrees of completeness. In these 173 replies, 83 pregnancies occurred following Caesarean section. There were 34 vaginal deliveries, 28 Caesarean deliveries and 7 were still pregnant at the time of enquiry. Spontaneous abortion occurred 12 times (14·5 per cent), therapeutic abortion twice and threatened abortion 5 times. The perinatal mortality was four.

One hundred and twenty-seven patients answered the question about sterility following operation. One hundred and ten were voluntarily sterile (including sterilization), 17 were involuntarily sterile. [There appears to be an arithmetical discrepancy between the number of pregnancies and the number of answers on sterility. The reviewer wonders whether some of the patients had had more than one pregnancy after Caesarean section, or whether some of the patients had had one pregnancy subsequently and then were voluntarily avoiding conception.]

Menstruation following Caesarean operation was reported as normal in 100 cases; menorrhagia, 24; polymenorrhoea, 8; oligomenorrhoea, 12; dysmenorrhoea, 7; and irregular periods, 1. The psychological status (patient's assessment)—normal, 94; nervous stress and depression, 40; marital harmony affected adversely, 5; lessened libido, 3; increased libido, 1.

[It is difficult to assess the value of a report on data supplied by the patients only in the form of a questionnaire. The number of replies—173 out of 255 patients—leaves a wide margin for discrepancies to occur. It is apparent, however, that voluntary sterility occurred in many cases following Caesarean section for one reason or another. Involuntary sterility was a comparatively minor factor, however.]

L. Woodrow Cox

MATERNAL MORTALITY

292. **Maternal Mortality (A Review of Maternal Mortality in N.W. Maternity Hospital, Bombay, During the Period of Five Years from 1953–1957).**

By N. D. MOTASHAW and M. V. JADHAV. *J. Obstet. Gynaec., India.*, **10**, 332–344. Mar. 1960. 10 tables. 14 refs.

A review is made of the maternal mortality in the N.W. Maternity Hospital, Bombay, during a five-year period. Over these years, the mortality remained stationary at 4·5 per 1,000.

Of the 218 deaths, 57 (26 per cent) were attributed to anaemia. The haemoglobin readings of the fatal cases ranged from 10 to 28 per cent. The majority were admitted as emergencies in labour, but antenatal care had been quite inadequate amongst the booked cases. With one exception, all deaths from anaemia were regarded as avoidable.

The 26 deaths from toxaemia, mostly eclampsia, accounted for 12 per cent of the total. One of the greatest difficulties lay in the fact that many women, having ensured a hospital confinement by one antenatal attendance, re-appeared only in eclampsia. The majority had no antenatal care.

Haemorrhage accounted for 43 deaths or 20 per cent of the total. Seven were due to placenta praevia, in which injudicious delay in operation was an important factor. Accidental haemorrhage accounted for 9, and postpartum haemorrhage for 17 cases. There were 8 ruptured uteri, caused mainly by attempts made at operative delivery outside hospital. Apart from this 42 deaths were due directly to operative interference, although there

may have been other contributory factors, and it is in this group that the largest proportion of deaths is attributed to faulty medical judgment.

Of the operative deaths, and those due to haemorrhage 87 per cent were preventable, the responsibility factor being divided equally between patient and doctor.

Two deaths followed anaesthesia, and comment is made on the fact that obstetric anaesthesia is so often left to the unskilled anaesthetist. There were 7 deaths from pulmonary embolus.

Poor social conditions plus failure of the patient to accept adequate antenatal care, due to ignorance, were the main factors underlying the majority of deaths. Anaemia took the highest toll.

John McKiddie

GYNAECOLOGY

293. **A Replacement for the Vaginal Douche.**

By S. G. BERKOW. *Obstet. and Gynec.*, **15,** 773–777. June 1960. 3 figs. 1 ref.

Vaginal douching, as normally practised, has many shortcomings, being relatively ineffective and sometimes dangerous.

To enhance the mechanical cleansing of the vagina two ingredients are combined by the author to promote spreading of the solution on the vaginal mucosa and to maintain active contact, and an inert, non-toxic aerosol propellant to enhance the action. One ingredient is cetyltrimethylammonium bromide, a detergent with bacteriocidal properties. The second agent is ethoxylated lanolin alcohol which maintains prolonged contact between the first agent and the vaginal mucosa. Lactic acid is included to maintain a pH of 5·0. Tetrafleurodichlorothane is the aerosol. The solution is enclosed in a special container with a plastic nozzle 1¾ inches in length. The nozzle has 4 openings, ejecting angulated streams.

The aerosol spray is used for 2 seconds, and has proved a safe and effective replacement for the vaginal douche.

J. G. Dumoulin

294. **Mechanisms of Uterine Support and Pathogenesis of Uterine Prolapse.**

By R. F. PORGES, J. C. PORGES and G. BLINICK. *Obstet. and Gynec.*, **15,** 711–726. June 1960. 8 figs. 24 refs.

The authors point out some of the misconceptions concerning the supports of the uterus. Fundamentally, there are two types of uterine support. In virgins and nulliparous women the uterus is maintained in its position by the contractions and tonus of the intact levator ani muscle, which has the sphincteric capacity to close almost completely the genital hiatus. During this time in a woman's life the endopelvic connective tissue exists as a mere loose, areolar connective tissue that is in no way able to withstand the force of intra-abdominal pressure.

During parturition, the levator diaphragm is usually damaged resulting in permanent enlargement of the genital hiatus, and the sphincter mechanism is replaced in the parous woman by the system of overlapping structures forming the so-called "pelvic valve". The latter depends on hypertrophy and fibrous condensations of the endopelvic connective tissue and anterior vaginal wall.

The levator muscles may undergo one of 3 types of alteration. It may be lacerated in the region of the perineum and rectum, it may be partly torn from its attachment to the symphysis or the entire muscle may become atrophic and funnel-shaped. If these things happen, the cardinal ligaments will become secondarily elongated and thickened. The idea that the cardinal and other ligaments normally suspend the uterus is wrong, and this only really happens in cases of procidentia.

J. G. Dumoulin

DISORDERS OF FUNCTION

295. **Biological Effects of the New Progestogens. Descriptions of Their Structure and Actions.** (Effetti biologici dei nuovi progestativi. Rapporti fra struttura e funzione.)

By G. SALA. *Ann. Ostet. Ginec.*, **82,** 321. Apr. 1960. 5 figs. 44 refs.

Until 1938 it was believed that only progesterone itself was capable of progestational activity. In that year, 17-alpha-ethinyl testosterone (Aethisterone) was discovered and shown to possess oral progestational activity.

Up to October, 1959, 34 compounds were shown to be progestogens, activity varying from 0·11 to 100 times that of progesterone. These substances have been shown to produce in varying degrees the following effects: progestational activity, including Clauberg's test in the pre-puberal rabbit, variations in uterine carbonic anhydrase and maintenance of pregnancy in the ovariectomized animal; anti-ovulatory action, anti-gonadotrophic action and secondary endocrine effects such as androgenic and oestrogenic activity and corticoid action.

Small alterations in the chemical structure of these new products may lead to profound changes in their endocrine effects.

Josephine Barnes

296. **Psychomotor Changes During the Menstrual Cycle** (Psychomotorische Veränderungen im Verlauf des Menstruationscyclus.)

By G. MARTIUS and G. GRUSON. *Arch. Gynäk.*, **192,** 464–482. 1960. 4 tables. 31 figs. 11 refs.

Twenty-four women aged between 19 and 30 years and menstruating regularly were studied during one or several menstrual cycles while basal temperatures were recorded daily. The women were asked to write on the mechanical writing scales by Steinwachs every second or third day and 315 writing pressure curves were thus obtained. The following features in these curves were evaluated: writing time in seconds, basal plateau formation (numbers per word), mean maximum pressures at start and end of

curve, minimum, mean and maximum amplitudes, signs of inhibition and disinhibition, and variability of curves. It appeared that there were three different types of response:

Group I, comprising 10 women, showed distinct changes of an evenly increasing psychomotor disinhibition and increase in tension in the first half of the cycle followed by psychomotor inhibition and increasing disturbance of co-ordination after follicular rupture.

Group II (10 women) showed similar changes in the second half of the cycle but to a much lesser degree and the psychomotor state in the first half of the cycle was also characterized by less disturbance. The curves thus obtained showed less pronounced cyclical variations.

Group III (3 women) showed distinct cyclical psychomotor variations, but their curves were the reverse of those obtained in Groups II and III.

One woman exhibited no cyclical variations in writing pressure curves and it was later shown that despite regular menstruation her cycles were anovular.

The authors conclude from their studies that the maximum performance of muscular functions and skill is associated with the first half of the cycle in the majority of women. The experience of female athletes, e.g., tennis champions, that their performance improves directly after the onset of menstruation and that this improvement is maintained up to the time of ovulation has thus been confirmed experimentally. It is also concluded that administration of ovarian hormones during the premenstrual phase with a view to postponing menstruation till after an athletic event is ill-advised. In order to increase physical performance the premenstruum should be shortened and not prolonged.

Comparing the types of curves with personality patterns and physical characteristics of the persons in experiment showed that the women in Group I were of the "schizothymic or leptosomic" type. Such women are prone to functional gynaecological disorders, highly excitable and easily exhausted. The women in Group II were of the cyclothymic type, rarely affected by gynaecological disorders, and Group III women belonged to the android type.

Erica Wachtel

297. **The Role of Noradrenaline in Regulating Disorders of Uterine Function.** (Die Rolle des Noradrenalin bei der Regelung der gestörten Wehentätigkeit.)

By M. TELKO. *Zbl. Gynäk.*, **82**, 817–827. May 28, 1960. 13 figs. 15 refs.

It is known that noradrenaline (N.) causes the human uterus to contract both *in vitro* and *in vivo*. As this has not been put to practical use so far, the author studied the effects of intravenous N. drips in a series of 57 patients in labour. One mg. of N. was added to 500 ml. of Dextran or 5 per cent glucose. The infusion was given at a rate of 10–60 drops per minute, depending on the response of the individual patient. Recordings of uterine action were made with a Lorand tocograph. The blood pressure and the foetal heart were checked every 3–5 minutes.

In 25 patients in labour who were suffering from primary or secondary inertia, it was found that N. invariably stimulated uterine contractions. It caused a temporary increase in uterine muscle tone and established regular contractions of high amplitude and frequency. Nineteen patients had a spontaneous delivery and six required forceps.

In 10 patients with inco-ordinate uterine action N. used in conjunction with "Largactil" corrected uterine function. Seven patients delivered spontaneously and three required forceps.

In a few patients "Largactil" was used as an analgesic and was followed by uterine inertia. Adequate uterine contractions were brought about by means of N. Six patients so treated delivered spontaneously.

The author observed that in cases of uterine inertia where synthetic oxytocin ("Syntocinon") failed to have effect, N. was always capable of re-establishing uterine action. He considers that N. is particularly suitable in this type of case, provided there are no contra-indications, such as toxaemia or foetal anoxia.

Bruce Eton

NEW GROWTHS OF THE REPRODUCTIVE ORGANS

298. **Cresyl Violet Staining in Exfoliate Gynecological Cytology.**

By M. MASIN and F. MASIN. *Obstet. and Gynec.*, **15**, 702–710. June 1960. 8 figs. 26 refs.

A short staining technique for routine microscopy, using cresyl violet in acetate buffer at pH 4·0 with subsequent dehydration and differentiation by acetone has been developed by the authors. The method is simple, the technique is rapid and remarkable clarity of morphological cellular detail is obtained. Also, one gets valuable information about the distribution of basophilic and metachromatic substances.

J. G. Dumoulin

299. **Melanoma of the Vulva.**

By R. E. SYMMONDS, J. H. PRATT and M. B. DOCKERTY. *Obstet. and Gynec.*, **15**, 543–553. May 1960. 2 tables. 6 figs. 16 refs.

Nineteen cases of melanoma of the vulva encountered at the Mayo Clinic form the basis of this report. Four received treatment elsewhere, and are excluded from the detailed study. Of the remaining 15, 11 had been operated on 5 years or more before the study, of which 6 survived: 3 of the 6 died subsequently of metastases.

A primary radical vulvectomy with bilateral dissection of inguinal and femoral nodes seems to give the best results. It was not possible to evaluate prophylactic or palliative post-operative radiation.

Melanomas were found in 6·1 per cent of malignant lesions of the vulva encountered. The majority of melanomas could be prevented by wide surgical removal of all non-hairy moles from areas subject to repeated trauma and irritation, and this can easily be done in the vulval region.

J. G. Dumoulin

300. **Primary Carcinoma of the Vagina.**

By S. L. MARCUS. *Obstet. and Gynec.*, **15**, 673–689. June 1960. 10 tables. 5 figs. 53 refs.

Twenty-three cases of primary carcinoma of the vagina, all of squamous-cell type, treated over the past 25 years are reviewed. Their average age was 64 years and they tended to have a late menopause. The lesion is uncommon in Negroes and Jews.

The anterior wall was the most common site when the lesions were predominantly in the lower third, whereas the posterior wall lesions were commonest in the upper vagina. Prognosis depended not on the size of the tumour or the degree of differentiation but on the dosage of irradiation, the radiosensitivity of the lesion and its location. Lesions of the lower third of the anterior vaginal wall seemed to have a poorer prognosis. Radical surgery was not used although one case was successfully treated by a combination of irradiation and inguinal lymphadenectomy. The irradiation treatment deemed best is a combination of X-ray and radium. *J. G. Dumouiin*

301. **Clinical Significance of the Diagnosis of Uterine Chorion-Epithelioma According to Data of the Obstetrical and Gynaecological Department of the Stalin Medical Institute.** (Klinika i diagnostika chorioepiteliomy matki po materialam Akushersko-Ginekologiczesko Kliniki Stalinskogo Medicinskogo Instituta.)

By J. M. LANDAU. *Akuš. i. Ginek.*, No. 3, 25–27. 1960. 14 refs.

During the period of 22 years ending in 1956 there were 22 cases of chorionepithelioma in the Stalin Institute, an incidence of 2·37 per cent of all patients operated on for obstetrical and gynaecological disorders. The patients ages ranged from 20 to 48.

Before admission the diagnosis was at fault in one-third of the cases. The main causes of error were: inadequate acquaintance of medical personnel with the disease, difficult access to histopathological investigations, underestimation and misinterpretation of hormonal shifts.

The basic signs of the disease are bleeding and pain; often both are present. The main preceding histories are those of hydatidiform mole, miscarriages and multiple pregnancies. The possibility of chorionepithelioma must be borne in mind in every case of evacuation of the uterus, especially if bleeding recurs, or if there are signs of ectopic gestation. Aschheim-Zondek and Friedman tests, particularly with diluted urine, are of assistance but are not pathognomic because even negative tests with undiluted urine may be erroneous. In cases of difficulty boiling the suspected urine for 15 minutes may be advantageous. Histopathology combined with biological tests should be the method of choice. Early diagnosis leads to successful treatment, and there was a five-fold decrease in mortality since 1928 when the Aschheim-Zondek test was introduced. *E. W. Collis*

302. **Observations on Diathermic Coagulation of Cervical Erosions.** (La diatermocoagulazione nel trattamento della lesioni della portio.)

By A. RUSSO. *Minerva ginec.* (*Torino*), **12**, 159–165. Feb. 15, 1960.

Ideally all lesions of the cervix should be examined by the colposcope or by cytology to exclude malignant disease. Schiller's Lugol-iodine test defines the iodo-negative areas which require treatment, but it is better to extend the area 1 to 2 mm. on to the stratified layer. Coagulation must not be intensified to the point of charring and great caution is needed in attacking the endocervix as stenosis, deep cicatrix or secondary haemorrhage can easily be produced by massive or too deep coagulation. The same applies to conization. Ovulae nabothi are best dealt with by acupuncture for which the current is reduced to compensate for the finer terminal used. Many so-called erosions are really ectropions due to old cervical tears and are better treated by trachelorrhaphy or amputation. Some cases of endocervicitis can however be given light cautery and sulphonamide creams.

A large percentage of erosions can be given outpatient treatment on the above lines, which saves time and beds and domestic disturbance. There is no point in combining this treatment with dilatation and curettage; in fact it is a disadvantage unless there are independent indications for the latter. No anaesthetic is needed (except perhaps a sedative), but treatment should begin with the relatively insensitive posterior lip. One treatment is usually sufficient, but it can be repeated in two months when all cases should be routinely reviewed. It is better not to treat just before the period is due as this increases the slight chance of haemorrhage. The patient is cautioned to abstain from sexual contact for six weeks and warned about the possibility of "spotting" 10 to 14 days after treatment when the eschars separate.

W. C. Spackman

303. **Intraepithelial Epithelioma of the Cervix.** (Le problème actuel de l'épithélioma intra-épithelial du col utérin.)

By P. FUNCK-BRENTANO. *Gynéc. et Obstét.*, **59**, 5–17. 1960. 22 refs.

In a short review of the history of this condition the author states that it was only in 1947 that the French first became properly aware of it. He prefers his title to the term carcinoma *in situ*.

The diagnosis rests on three anomalies of the cells: (*a*) Anaplasia, consisting of irregularity of the height and form of the basophil cells, diminution or disappearance of glycogen and an increase in the proportion of the nucleus to the cytoplasm. (*b*) Atypical nuclei, large in size with multiple lobules. (*c*) Anomalies of proliferation, such as mitoses in excess, abnormal positioning of chromosomes and mitoses in superficial layers.

The author considers that only reversible lesions merit the name of intra-epithelial epithelioma. He discusses the potential malignancy of the condition, and after quoting many authorities comes to the conclusion that malignant change is a possibility, but that it only occurs after a latent period of 10 years on the average.

Special methods of diagnosis include: (1) colpo-

cytology, (2) Schiller's test and (3) colposcopy, and he discusses the value of these methods.

Treatment is described. If the diagnosis is uncertain it is safe to wait. If the diagnosis is certain and the patient is more than 45 years old total hysterectomy with bilateral salpingo-oöphorectomy is performed; if the patient is between 35 and 45 the ovaries may be conserved. In a woman under 35 years of age who wished for children amputation of the cervix is carried out, either vaginally or abdominally by Huguier's method, although the author points out that amputation of the cervix greatly increases the risk of abortion. When the intra-epithelial epithelioma encroaches on the mucosa of the upper portion of the vagina it is necessary to remove a cuff of vagina, and every piece removed must be examined very carefully histologically, and if an invasive element is found Wertheim's hysterectomy is subsequently performed. The role of radiotherapy is also briefly discussed.

Elliot E. Philipp

304. **Role of the Halo Cell in Cervical Cancerigenesis.** By T. E. AYRE. *Obstet. and Gynec.*, **15**, 481–491. Apr. 1960. 16 figs. 13 refs.

The halo cell of the human cervix appears to represent an extremely early transformation stage from chronic infections to malignant disease created under such environmental influences as increased oestrogenic activity, over-production of cervical mucus, scar tissue deprivation of oxygen supply and resultant virus activation. The halo cell may represent the transient virus-manifest stage of premalignancy as progressive morphological cell changes to infiltrating malignancy transpire.

Halo cells are atypical cells which exhibit a large, clear perinuclear zone, exfoliating singly or in groups and observed most consistently in direct cell scrapings from the cervix. They seem to be found exclusively at the border line between chronic infection activity and early cell manifestations of premalignancy. The author develops the theory that halo cells are caused by some nucleic acid-viral infections activity in an oestrogenic environment which produces derangement of cell metabolism and orderly replication of cells, and that they are probably a mutant deviation towards malignant cell growth.

J. G. Dumoulin

305. **Evaluation of Radiation Response.** By A. M. AGNEW, H. K. FIDLER and D. A. BOYES. *Amer. J. Obstet. Gynec.*, **79**, 698–699. Apr. 1960. 3 refs.

Radiation response studies using the Ruth Graham criteria were made on patients with cancer of the cervix. Of 107 patients who were followed up to 5 years or more 76 were judged to have a good response, and in this group the 5-year survival rate was 70 per cent. Thirty-one had a poor response and a 5-year survival rate of 26 per cent. The smears were taken 1 week after the first insertion of radium, 2 weeks after the second and 1 week after the third insertion. Thirty-one smears showed a good response after the first application of radium, 31 became good after the second, and 14 after the third. It therefore seems that a decision regarding the efficacy of radiation cannot be made until after the full course has been given.

F. J. Browne

306. **Hilus Cell Tumour of the Ovary.** By E. R. NOVAK and R. F. MATTINGLY. *Obstet. and Gynec.*, **15**, 425–432. Apr. 1960. 2 tables. 4 figs. 28 refs.

To the 10 cases reported in the literature of hilus cell tumour of the ovary, the authors have added 8 more cases from the Ovarian Tumor Registry. This is a lipoid tumour, usually arising in the hilus of the ovary, and possessing certain endocrine effects. Most authors believe that hilus cells are identical with the interstitial cells of Leydig found in the testis. Hirsutism is nearly always found in hilus cell tumours as is amenorrhoea, although post-menopausal bleeding is by no means rare. Elevated 17-ketosteroids occurs in about half the cases in which it has been estimated. The lesions are benign and the clinical stigmata completely reversible by operation. In cases where the endometrium has been studied, hyperplasia is found. Reinke crystals, so highly praised as a diagnostic criterion, are found in less than 50 per cent of cases, but their presence almost certainly suggests the tumour is of hilus cell origin.

J. G. Dumoulin

307. **Malignant Solid Teratoma of the Ovary.** By K. BENIRSCHKE, C. EASTERDAY and D. ABRAMSON. *Obstet. and Gynec.*, **15**, 512–521. Apr. 1960. 13 figs. 9 refs.

Three patients are described whose post-partum course was complicated by the rapid development of large solid teratomas. These tumours spread widely and caused death of 2 patients, the first having evidence of persistent peritoneal growth. The teratomas were unusual in that their gross appearance was that of a malignant tumour; however, histological study of tumours and their recurrences showed perfect differentiation of all tissue with many organoid structures being present.

The important clinical findings are the rapidity of growth, their association with pregnancy or presence in women of the reproductive age, the frequency of adhesions to surrounding structures, and the characteristic gross appearance—that is, largely solid, red in colour with yellow stipples throughout and innumerable small cysts containing mucoid or clear fluid. Such tumours tend to be very malignant although sometimes there is considerable variability in their behaviour. Treatment consists of early primary radical removal.

J. G. Dumoulin

308. **Final Contribution to the Problem of Histogenesis in Krukenberg Tumours.** (Ulteriore contributo al problema istogenetico del tumore di Krukenberg.) By G. B. CANDIANI. *Ann. Ostet. Ginec.*, **82**, 211. Mar. 1960. 24 figs. 12 refs.

A careful study has been made of Krukenberg tumours. It is noted that they contain epithelial elements that are

intestinal in character. The author believes that the primary lesion in the stomach arises from heterotopic intestinal plaques in the gastric mucosa which undergo cancerous change and form the starting point of secondary metastasis.

Cellular elements undergoing mucoid degeneration can be found in the connective tissue stroma of the gastric tumour, in the ovarian parenchyma and in the infundibulo-pelvic ligaments. These tissues all show similar staining properties with mucicarmine stains and this strengthens the theory of retrograde lymphatic spread.

Josephine Barnes

309. **Ovarian Metastasis of Breast Carcinoma.**

By N. TURKSOY. *Obstet. and Gynec.*, **15,** 573–578. May 1960. 2 tables. 2 figs. 10 refs.

Twenty-six castration and 19 autopsy reports on ovaries of patients with primary carcinoma of the breast at the hospital of the University of Pennsylvania were studied. Ovarian metastases were found in 8 of 26 surgically removed ovaries (30·7 per cent) and in 8 of 19 autopsy cases (42 per cent). The metastatic involvement was bilateral in all 8 of the autopsy cases and in 5 of the 8 positive castration specimens. Even though the excised ovaries are grossly normal, they may contain metastases on microscopical examination.

J. G. Dumoulin

310. **Conservative Treatment of Endometriosis.**

By H. H. THOMAS. *Obstet. and Gynec.*, **15,** 498–503. Apr. 1960. 4 refs.

This report concerns observations on 35 women with endometriosis. The long-acting steroid esters Delalutin (17-alpha-hydroxyprogesterone caproate) and Delestrogen (estradiol valerate) were given in doses of 250 mg. Delalutin and 5 mg. Delestrogen twice a week by injection for 2–10 months.

Amenorrhoea was induced in all patients during the period of hormone injections, and pelvic pain and dysmenorrhoea were benefited in nearly all cases. The best results were attained in cases treated for longer than 3 months. There were no complications. The treatment seems effective and should be given further clinical evaluation.

J. G. Dumoulin

OPERATIONS

311. **A Defence of Promontorial Fixation (Sacral Hysteropexy).** (Zur Ehrenrettung der Promontorifixur.)

By H. NÖLLE. *Geburtsh. u. Frauenhelik.*, **20,** 479–487. May 1960. 4 tables. 12 refs.

The operation of sacral hysteropexy, suggested by Küstner in 1904, was recently condemned by German gynaecologists (*Zbl. Gynäk.*, 1959, **81,** 219). The author reports his own satisfactory experience with this operation, which he has used for the treatment of uterine prolapse (81 cases) and vault prolapse (3 cases). The operative mortality was nil and only minor post-operative complications occurred. The 3 cases of vault prolapse were free from recurrence 3 years after the operation; 70 of the 78 cases of uterine prolapse, which were followed for a period of 2–9 years after the operation, were well and free from recurrence. Twenty-four patients complained of stress incontinence and 20 were cured; in 12 of these cases sacral hysteropexy was combined with an anterior colporrhaphy. In these cases the operation commenced with the anterior colporrhaphy, but the stitches supporting the bladder and closing the anterior vaginal wall were only tied after the hysteropexy had been completed from the abdomen. Following promontorial fixation of the uterus 15 women became pregnant: in 9 of them the pregnancy ended normally; one woman was delivered by Caesarean section and it was observed that the uterus was connected to the sacral promontory by a band of connective tissue 2–3 cm. long. There were 5 abortions, but only 3 of them spontaneous.

[This operation and its results are similar to those described by Arthure and Savage, *J. Obstet. Gynaec. Brit. Emp.*, 1957, **64,** 355.]

Peter J. Huntingford

312. **Aetiology of Recurrence After Plastic Operations.** (Über die Ursache der Rezidive nach plastischen Operationen.)

By H.-J. WORASCHK. *Zbl. Gynäk.*, **82,** 700–705. May 7, 1960. 4 tables. 7 refs.

The success of vaginal plastic operations depends, according to the author, on the constitution of the patient, environmental factors, and the surgical procedure.

He reports on a series of 572 patients who underwent various types of colporrhaphy during the years 1952–1957. In response to a written request 340 patients (60 per cent) attended for follow-up examination. Very strict criteria were adopted for the assessment of results. A small cystocele, rectocele, or minor defects of the pelvic floor were regarded as recurrence, even if the patient was entirely free from symptoms and satisfied with the result of the operation. On this basis the author found a gross recurrence rate of 45·3 per cent. If however the functional result alone was considered, the rate was 28·8 per cent.

More than 80 per cent of patients regarded hard work as the cause of their prolapse; only 17 per cent attributed it to difficult labours.

The recurrence rate averaged about 30 per cent, irrespective of age group, occupation, parity and incidence of forceps delivery. Statistical analysis of the results revealed however that the recurrence rate was better if the patients were operated early: it was 23 per cent amongst those operated within a year of the onset of the complaint, whereas it was about 30 per cent amongst those operated after 2 or more years.

Assessment of the various surgical procedures showed that the recurrence rate was 35 per cent after anterior and posterior colporrhaphy, whereas it was 22 per cent,

if the uterus was removed vaginally at the same time. The length of stay in hospital following operation was related to the recurrence rate, as it was higher in patients discharged after the 20th post-operative day than amongst those discharged earlier.

Comparison of the results in patients operated by junior and senior staff showed no difference in the recurrence rate.

Two hundred and fifty-six of the 340 patients had initially suffered from various degrees of urinary incontinence. Even regarding this symptom the recurrence or failure rate was 30 per cent.

Bruce Eton

THE ROYAL SOCIETY OF MEDICINE

The following awards have recently been made by the Council of the Society:

Blair Bell Medallist, 1960: Professor F. J. Browne. The Blair Bell Medal is awarded quinquennially for the advancement of science in gynaecology and/or obstetrics in the preceding five years.

Nichols Fellowship, 1960–61: Dr. Fred Benjamin of Cape Town University for his work on "Glucose Tolerance in Dysfunctional Bleeding at the Time of the Climacteric and in Carcinoma of the Endometrium". This Fellowship is awarded triennially for researches to advance knowledge in Obstetrics and Gynaecology.

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For further information apply to Dr. Roberto Ascanio, Sociedad de Obstetricia y Ginecologia, Apartado 7332 (San Martin), Caracas, Venezuela.

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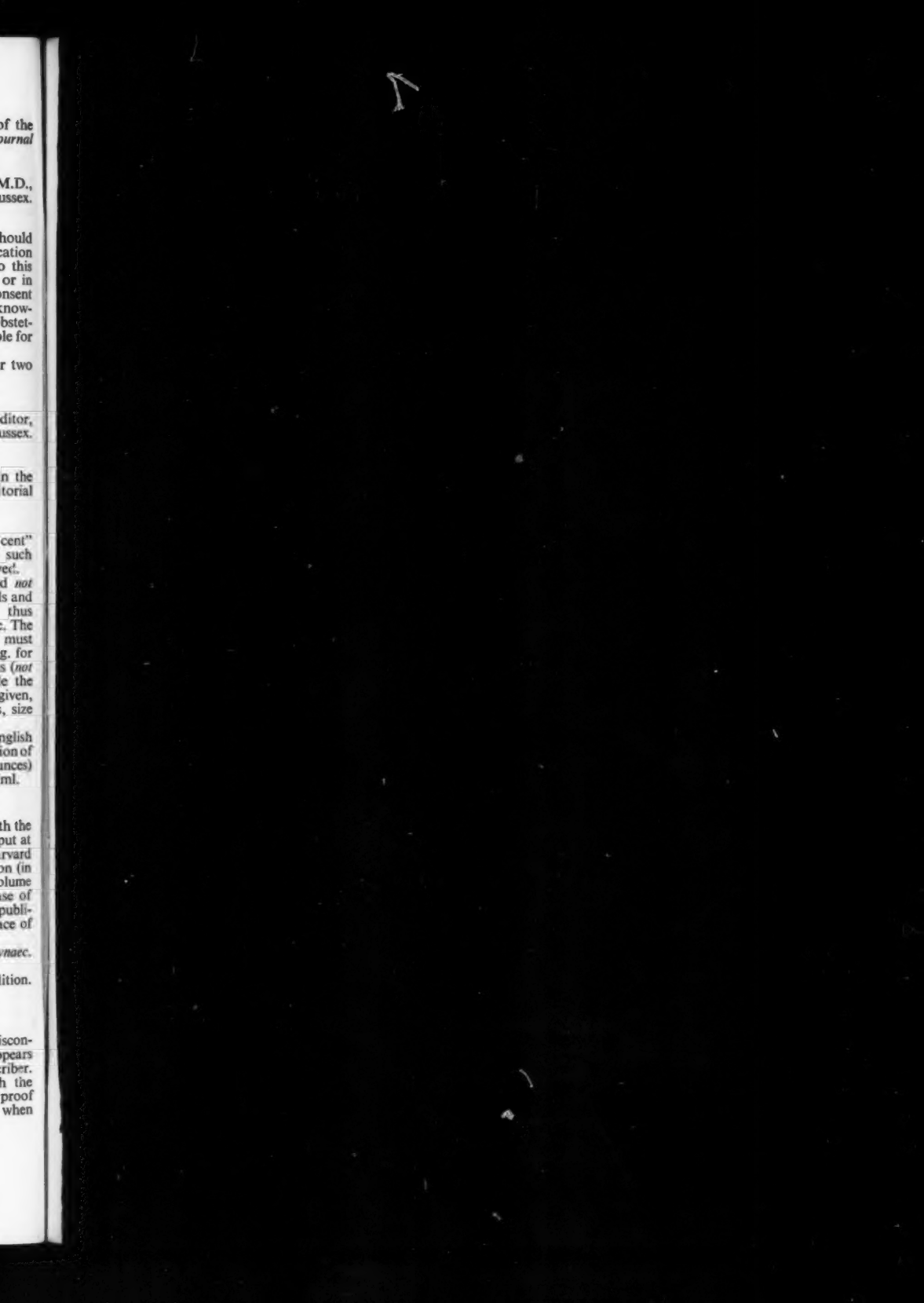
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